CUTANEOUS MANIFESTATIONS *of the* MALIGNANT LYMPHOMAS

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Edited by

ARTHUR C. CURTIS, M.D.

Chairman, Department of Dermatology and Syphilology
University of Michigan Medical School
Ann Arbor, Michigan



Pruriginous lesion (Hodgkin's) *Pruriginous lesions or* prurigo like papules often signify Hodgkin's disease The pruritus is intense, scratching denudes the apices of the papules leaving them red bleeding, and infected



Scalp nodules in lymphosarcoma Lymphosarcoma may be suggested by lesions that also occur in leukemia and Hodgkin's disease Various sized red bluish or skin colored specific nodules which tend to regress spontaneously may be numerous

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of the MALIGNANT LYMPHOMAS

By

SAMUEL M. BLUEFARB, B.S., M.D., F.A.C.P.

Associate Professor of Dermatology, Northwestern University Medical School

Attending Dermatologist and Chairman, Department of Dermatology, Cook County Hospital

Attending Dermatologist, Veterans Administration Research Hospital

Senior Attending Staff, Chicago Wesley Memorial Hospital, Chicago, Illinois

With an Introduction by

STEVEN O. SCHWARTZ, M.D.

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FOR RICHARD

INTRODUCTION

THIS VOLUME is the summation of more than 15 years of study and effort in a particular field of medicine To the careful student as well as to the casual reader it will be obvious that material so comprehensively gathered carefully evaluated meticulously documented and thoroughly studied can only be the result of a long period of gestation nourished by keen interest constant search vast experience and infinite patience By virtue of training background and study of a vast amount of clinical material Doctor Bluefarb is extraordinarily fitted for the task of writing *The Cutaneous Manifestations of the Malignant Lymphomas* This book in which the contents far exceed the promise of the title contains a discussion of treatment as well as other aspects of the lymphomas gathered from the spectrum of the most rare to the most frequent cutaneous manifestations of these diseases as described in the earliest to the most recent literature

The cutaneous manifestations of this large group of diseases which vary so widely both locally and systemically suggest fundamental differences in the underlying mechanism of cause and effect However one is impressed by certain similarities and common denominators which suggest that this group of diseases at present only linked nosologically may eventually be tied together by a common etiology Indeed upon perusal of this book one is so impressed by this observation that he is tempted to assume the skin to be capable of an even more varied form of response to similar stimuli than is ordinarily credited to this organ

This volume will serve to emphasize Doctor Bluefarb s teaching that the skin often serves to reflect the changes in the inter

nal milieu of the body, particularly changes in the reticuloendothelial organs Thus, the skin serves

To hold, as't were, the mirror up to nature"

STEVEN O SCHWARTZ, M D
Director Hematology C C H and
the Hektoen Institute for
Medical Research of the Cook County Hospital

PREFACE

This volume *The Cutaneous Manifestations of the Malignant Lymphomas,* is another in the series of monographs on the cutaneous manifestations of the reticuloendothelial system In this volume *The Malignant Lymphomas,* mycosis fungoides Hodgkin's disease and lymphosarcoma are included Because this series is devoted primarily to the cutaneous aspects of these diseases we have not attempted a detailed study of the various forms of lymphosarcoma The classification of the lymphosarcomas is best left to the cytologists The cutaneous manifestations of lymphosarcoma are essentially the same in the various forms

It is obvious that the most outstanding contribution which could be made to this field of medicine would be the discovery of the cause of these diseases However since this essential fact is not apparent at this time there may be some constructive value in collecting and correlating representative examples of the cutaneous manifestations and observations on the natural history of these diseases These facts may be of some diagnostic aid and more important may possibly suggest new methods of approach to the clarification of the heretofore obscure knowledge regarding the origin and clinical course of lymphomatous diseases

The cutaneous manifestations associated with diseases of the reticuloendothelial system constitute an *important link between* the fields of dermatology and internal medicine In many instances the cutaneous features are the first discernible signs of disease thus permitting a diagnosis to be made before lymphadenopathy splenomegaly hepatomegaly *or changes in* the peripheral blood picture become apparent

The skin is an excellent structure for study of reticuloendothelial system diseases since all gradations of involvement from

benign tumors, such as histiocytoma, to malignant tumors, such as lymphosarcoma, may be demonstrated The skin is also an excellent site for research regarding the cause of these diseases in determining which agents are capable of stimulating the reticuloendothelial system

Among the many who have aided me in preparing these volumes, I am most indebted to Arthur C Curtis, M D for his valuable suggestions, constant encouragement and for reading the manuscript and to Herbert Rattner, M D for reading the manuscript I am appreciative to Steven O Schwartz, M D, who is singularly qualified to write the introduction to this volume I am also indebted to Miss Sophie Price of the Medical Library Staff, Northwestern University Medical School, for verifying the bibliography, and to Miss Maude Walsh, Medical Photographer, Northwestern University Medical School, for preparing the photomicrographs

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GRANULOMA FUNGOIDES

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CUTANEOUS MANIFESTATIONS
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PART ONE

MYCOSIS FUNGOIDES
GRANULOMA FUNGOIDES

I.

DEFINITION

Mycosis fungoides is an uncommon chronic fatal disease of the reticuloendothelial system of the skin which may result in secondary involvement of the lymph nodes and internal organs Clinically the disease is manifested by three stages 1) erythema or eczema 2) infiltration lichenification and plaque formation and 3) tumors Pruritus is usually present in the first two stages Each stage has a variable morphologic picture and may be present for months or years although certain phases of the disease may never occur The tumors tend to ulcerate and the disease ultimately causes death

II.

SYNONYMS

1) Granuloma Fungoides (Auspitz–1885)
2) Granuloma Sarcomatodes (Naether)
3) Inflammatory Fungoid Neoplasm (Geber and Duhring–1879)
4) Ulcerative Scrofuloderma (Van Harlingen)
5) Eczema Tuberculatum (Wilson–1875)
6) Fibroma Fungoides (Tilbury Fox–1873)
7) Lymphodermia Perniciosa (Kaposi–1885)
8) Sarcomatosis Generalis (Kaposi–1886)
9) Lymphadénie Cutanée (Gillot–1869, Vidal–1881)
10) Multiple Sarcoma of the Skin (Hyde)
11) Lichen Hypertrophique (Hardy–1861)
12) Multiple Fungoid Papillomatous Tumors (Kobner–1864)
13) Dermo-Linfoadenoma Fungoide (di Amicis–1882)

III.

HISTORY

In 1806 Alibert (2a) described a 56 year old man with "une eruption furfuracee" which was followed by small smooth painless nodules of brown or normal skin color present on various parts of the body Forty of these nodules involved the face and successively involved the axillae groins popliteal fossae scrotum and inner aspects of the thighs The tumors were sessile and secreted a greenish ichorous humor" The skin was markedly insensible following sloughing and involution of the nodules Vesicles and bullae occasionally appeared The ulcers which followed nonhealing tumors were painful and emaciation diarrhea hyperpyrexia and hectic fever resulted in death five years after onset of the disease There was *no* autopsy The illustration plate although well produced does not show the tumor surface clearly but it was undoubtedly raw and granulating The largest tumor greater than a walnut" in size was present on the left cheek another half this size involved the chin and a third was situated *on the* upper lip while several small growths *apparently* covered by normal skin were scattered over the nose fo ehead and cheek Alibert stated that the tumors resembled "mushrooms" ("Des Morilles" "Morchella esculenta or those known as "agarics") but did not state whether this similarity was in size color shape consistency or rapidity of growth *He regarded* the condition as a form of yaws and in 1814 (2b) named it "pian fungoide" with the Latin synonym Frambesia Mycoides He did not believe he was describing a new disease but thought the case remarkable because of the occurrence of a *tropical* disease in a Frenchman who had never been *away* from Europe This disease is still known as Pian Yaws Frambesia

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tionnel de fixer irrévocablement les trois espèces suivantes" M. frambesioides identical with "pian" or yaws, M. fongoide and M. syphiloides, with which he identified the Scottish Sibbens. The anatomical aspect of Alibert's disease is a



2. Original case of mycosis fungoides described by Alibert (2a)

granuloma in the terminology of Virchow, and therein resembles not only yaws but lupus, tuberculosis and tertiary syphilis as well, according to Pye Smith (281). The malignant character of the disease, however, was recognized by Alibert (2c)

in the Dutch East Indies, Amboyna, Moluccas, Guinea Coast and among Negroes in the West Indies and elsewhere

In 1832 Alibert (2c) renamed the disease "mycosis" because of the "*mushroom-like*" appearance of the tumors but did not



1 Jean Louis Alibert (Centenaire de La Faculte de Medecine de Paris, 1794–1814, Par le Dr A Corlien Paris, 1896)

intend to suggest fungi as the causative agent He then put his previously described cases in the group Dermatoses Verolosés', a group which included only two "genera' syphilis and mycosis Of the latter genus he writes "il nous semble ra

to granulation tissue Further advances were made in Germany by Paltauf (265a) who demonstrated secondary involvement of internal organs although he believed that the disease first affected the skin He first called it a form of lymphosarcoma but later in a publication with Zumbusch (265e) based on studies of two necropsies concluded that there was no relationship with neoplasm and suggested classification with the infectious granulomas

The first American report was by Duhring (91) in 1879 He considered the disease to be an inflammatory new growth but did not believe his case to be the same as those described by Hardy (147) Bazin (17a) or Kobner (187a) However he considered it to be in the same category as those reported by Hebra (149) in 1872 and in 1874 He believed his case should be differentiated from those reported by Gillot (128) and Ranvier (286) and pathologically he considered the lesions to be inflammatory in the early stages but later assuming the appearance of sarcoma Heitzmann studied Duhring's case histologically and regarded it as sarcoma Other Americans who contributed to this subject in the late 19th century were Morrow (247) Hyde and Montgomery (162) Tilden (334) Blanc (34) and Stelwagon (321)

In Italy di Amicis (85) first described a case in 1882 and Stukovenkoff (327) reported the first Russian case in 1889 During this same period Kaposi (176b) classified the disease in the category of general sarcomas

A second form of mycosis fungoides was described by Vidal and Brocq (346c) in 1885 namely mycosis fungoides d'emblee" This type presents only the tumor stage and the first two stages do not occur It is our impression that this designation is a misnomer since these cases are nearly always lymphosarcoma (Bluefarb 38b) a subject discussed *more* fully under Pathogenesis (V)

A third form of the disease the "erythroderma" form was described by Hallopeau (145a) in 1892 This condition we also believe is not mycosis fungoides but a clinical *manifestation* of either chronic lymphocytic leukemia Hodgkin's disease

Knowledge of the histologic structure of mycosis fungoides was advanced by the research of Ranvier (286) and Hebra (149) In 1869 Gillot (128), in a thesis inspired largely by the work of Bazin (17a) and Ranvier (286), concluded that the disease was due to the development of reticular lymphoid tissue *in the skin* and, therefore, a cutaneous manifestation of the lymphoid diathesis He called the condition 'lymphadénie cutanée'

Clinical knowledge of mycosis fungoides was advanced by Bazin (17a) who, in 1851, observed three cases in which he recognized all manifestations and the three stages in the course of the disease He recognized mycosis fungoides to be a malignant condition distinct from carcinoma The credit for defining this disease as a special morbid process belongs largely to Bazin since he defined the particular type of lesion and named it Mycosis Fungoides' He differentiated the disease from syphilis but, unable to classify it, created the term 'di athesis fungoidique' Later, however, he believed it to be a form of leprosy and described several cases as "lepre-indigene" In 1876 Bazin (17b) again contributed to the clinical knowl edge with his classic description of the different phases of mycosis fungoides, although he accepted the lymphodermata theory with some reservations

Further studies by Barié (15) Debove (77) Demange (81) Desnos (84), Gaillard (119) Landouzy (194) and others confirmed the research of Gillot (128) and Ranvier (286) Vidal (346a) regarded it as a disease SUI GENERIS one patho logically midway between lymphadenie and sarcoma

While early studies of this disease were made by the French case reports began to appear in other countries In England Tilbury Fox (113) described "Fibroma fungoides" in 1873 and Wilson (364) Eczema tuberculatum" in 1875

The first German report was by Kobner (187a) in 1864 who after studying four cases independently advanced the theory of an inflammatory granulation tumor He described the disease as "papillomatous fungoid tumors of the skin" which he concluded were inflammatory and pointed out the resemblance

IV

ETIOLOGY

A Sex and Age

Mycosis fungoides appears to affect men more often than women although the sex predisposition is very slight. Sequeira (311b) found 37.8 per cent were women in a series of 74 cases and Gerwig (127) reported 38 per cent women among 602 patients. In analyzing 719 cases Heite and Socha (150) reported that the disease occurred in 255 women (43.36 per cent) of the 588 cases in which the sex was given. Lapiere (197a) noted an equal sex ratio and Thompson (332b) believed both sexes to be equally affected. However, in these studies no distinction was made between the classical, "erythroderma" or "d'emblee" types of mycosis fungoides. We have therefore classified the type of disease present in 427 cases in the literature which had sufficient data to be included in a statistical study.

TABLE I

SEX INCIDENCE

Type	*Number Cases*	*Men*	*Per Cent*	*Women*	*Per Cent*
Classical	308	177	57.5	131	42.5
D'Emblee	84	59	70.3	25	29.7
Erythroderma	35	26	74.3	9	25.7

The age at onset is variable, the "d'emblee" type having been reported in an eight month old infant by Serra *et al.* (313) and as late as the age of 86 years by Troxell (340) in a patient who first developed symptoms at 81 years of age. The occurrence in adolescence has been reported by Gastou and Sabareanu

or lymphosarcoma. A more detailed discussion appears under Pathogenesis (V).

Auspitz (11) advocated designating this disease "granuloma fungoides" rather than mycosis fungoides. This name would be preferable, since there is agreement that a mycotic element is not the causative agent, even though the etiology is still not known. Keim (179b) stated that since this misleading term, mycosis fungoides, has been in use more than 100 years it should be corrected, as the condition is not mycotic and, with present day irradiation therapy, the lesions seldom fungate. He noted that the term appears only in dermatologic literature and the dermatologist should, therefore, be condemned for continuing its use, without, at least, a qualifying adjective. In my opinion, the term granuloma fungoides is a more appropriate designation for this condition. However, the term mycosis fungoides is retained throughout this publication since it has preference because of continued usage.

TABLE IV

AVERAGE DURATION (YEARS)

Type	Men	Women	Average for Type
Classical	8 46	8 63	8 55
D'Emblee	3 15	3 37	3 24
Erythroderma	5 47	9 1	7 29

Although there are many reports in the older literature concerning the longevity of the parents of many mycosis fungoides patients Pernet (271a) was the first to record this fact A patient reported by Fraser (114a) had such a family history This observation however does not appear to be in accord with the experience of present day observers

B Occurrence in the Young

The majority of reports of mycosis fungoides occurring in young persons describe the "d emblee" type and are undoubtedly cases of lymphosarcoma

An eight month old girl who developed the d emblee" type during the first few days of life was described by Serra et al (313) Another case of this type reported by Decrop *et al* (78b) was in a 12 year old child who developed a tumor in the dorsal lumbar region This tumor which involved the spine and produced paraplegia responded favorably to roentgenotherapy

O Leary *et al* (258e) presented a man who first developed a lesion in the right groin at 12 years of age At the age of 24 years lesions appeared at the waist, and at friction points on the back Five or six years before examination at 49 years of age the lesions had begun to increase markedly in number He was also found to have diabetes mellitus and multiple thyroid adenomas for which he had had a thyroidectomy Roentgenogram of the thorax revealed infiltration of the left lung There were 15 per cent eosinophils in the peripheral blood and histologic examination of an infiltrated cutaneous plaque showed a polymorphous infiltrate and epithelial

(123) in a 15 year old girl, by Sereni (312) in a 16 year old girl and by Vollmer (347) in a 17 year old girl.

The average age at onset, according to Thomson (332b), is 45 years. In tabulating 427 cases, we found the average age, when classified according to types, to be somewhat older.

TABLE II

AVERAGE AGE (YEARS)

Type	*Men*	*Women*	*Average Age for Type*
Classical	51.6	47.5	49.4
"D'Emblee"	50.9	47.6	49.2
"Erythroderma"	52.0	57.3	54.6

TABLE III

AGE ACCORDING TO DECADES

Type	*Classical*			*"D'Emblee"*			*Erythroderma*		
Age Group	*Men*	*Women*	*Total*	*Men*	*Women*	*Total*	*Men*	*Women*	*Total*
0-9	0	0	0	0	1	1	0	0	0
10-19	2	3	5	2	1	3	0	0	0
20-29	7	14	21	2	3	5	1	0	1
30-39	22	22	44	8	2	10	5	0	5
40-49	38	28	66	16	4	20	5	4	9
50-59	49	37	86	6	6	12	7	1	8
60-69	35	20	55	12	6	18	4	2	6
70-79	17	6	23	4	1	5	4	1	5
80-89	2	0	2	4	0	4	0	0	0

Poulsen (278) found the duration of illness, prior to admission to the hospital, varied from one to seven years, although in one case the duration was from 12 to 15 years, among the six fatal cases. Our average duration when classified according to type, was as follows.

TABLE IV

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The average age at onset, according to Thomson (332b), is 45 years In tabulating 427 cases, we found the average age, when classified according to types, to be somewhat older

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Type	*Men*	*Women*	*Average Age for Type*
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"Erythroderma"	52 0	57 3	54 6

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0 9	0	0	0	0	1	1	0	0	0
10 19	2	3	5	2	1	3	0	0	0
20 29	7	14	21	2	3	5	1	0	1
30 39	22	22	44	8	2	10	5	0	5
40–49	38	28	66	16	4	20	5	4	9
50 59	49	37	86	6	6	12	7	1	8
60–69	35	20	55	12	6	18	4	2	6
70 79	17	6	23	4	1	5	4	1	5
80 89	2	0	2	4	0	4	0	0	0

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10–19	2	3	5	2	1	3	0	0	0
20–29	7	14	21	2	3	5	1	0	1
30–39	22	22	44	8	2	10	5	0	5
40–49	38	28	66	16	4	20	5	4	9
50–59	49	37	86	6	6	12	7	1	8
60–69	35	20	55	12	6	18	4	2	6
70–79	17	6	23	4	1	5	4	1	5
80–89	2	0	2	4	0	4	0	0	0

Poulsen (278) found the duration of illness, prior to admission to the hospital, varied from one to seven years, although in one case the duration was from 12 to 15 years, among the six fatal cases. Our average duration, when classified according to type, was as follows

sis There were characteristically circinate and gyrate lesions on the trunk thighs and arms which were scaling, macular and slightly pruritic

The case of a 40 year old woman who presented the pre mycotic and infiltrative stages of mycosis fungoides from the onset of the disease 16 years previously, was reported by Traub (338a) She had first developed a large erythematous plaque on one side of the face which was followed by highly infiltrative lesions which had been present constantly Downing (89) described a 30 year old man who first developed a "flaking" cutaneous lesion on the jaw which appeared at irregular intervals One year later an elliptical red patch which was studded with minute nodules appeared on the chest. The cutaneous surface in this area was at first moist but later the nipples became painful and then fissured and tender However these symptoms disappeared within a few weeks and the skin became a network of geographic patches which appeared intermittently" The hands feet and fleshy portions of the buttocks were not affected and there was only moderate involvement of the chest and back, while the abdominal area was most severely involved.

Kovacs (190) reported an 18 year old girl who had mycosis fungoides for seven years Roentgenogram revealed "mycosis fungoides of the lungs" and autopsy confirmed this finding A 30 year old Negro who had mycosis fungoides for one year was described by Strobel and Hazen (326 case 2) Portnoy s (276 case 2) patient was a 17 year old boy who had mycosis fungoides "d emblee" for one month Sereni (312) described a 16 year old girl who had the d emblee" type for two and one half years before her death A 15 year old girl was described by Gastou and Sabareanu (123)

The impression remains that the majority of patients in the first two decades of life have the "d emblee" type In our opinion these cases represent a form of lymphosarcoma or rarely Hodgkins disease and should be included in these categories rather than with mycosis fungoides

changes consistent with early mycosis fungoides. Michelson (237) noted that all the cutaneous lesions present in this patient were round or oval and stated that round lesions occur almost constantly in premycotic mycosis fungoides while linear lesions seldom occur in this stage.

A 13 year old girl with universal alopecia was described by Giovannini (130). The scalp, axillary, pubic, eyebrow and eyelash hair fell out rapidly one week after severe influenza. Eczematous premycotic cutaneous lesions, most marked on the upper thorax, appeared six months later. Histologic examination revealed cellular infiltration around the hair follicles and cutaneous glands with hypertrophy and relaxation of the annular fiber bundles joining the hair follicles present in the areas most involved by total alopecia. In the areas having premycotic lesions, the cellular infiltration was more abundant and was stretched into the upper cutis. She died from pulmonary tuberculosis ten years after the cutaneous symptoms appeared but Giovannini was unable to determine whether the cutaneous infiltration followed the alopecia or the mycosis fungoides.

Vollmer (347) described a 17 year old girl who presented symmetrical infiltrated plaques on the hands, feet, knees and elbows which were severely pruritic, especially at night. A 17 year old boy whose cutaneous lesions were considered to be "eczema" for eight years before he developed fungating nodules up to seven cms. in diameter on the right leg was reported by Markowitz (234). The case of a 19 year old girl who had eczematous-like cutaneous lesions for four months before they became typical mycosis fungoides tumors was described by van Runckelen (345). A 20 year old woman reported by Quinn (283) had fungoid tumors involving all cutaneous areas except the palms and soles which had been present for one year. An eczematoid eruption had first appeared three years before the rapid development of fungoid lesions following the injection of silvarsan. The 25 year old man presented by Klauder (184a) had cutaneous lesions since the age of 14 years which had been considered to be parapsoria

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C Familial Incidence

A familial incidence is not rare in the lymphoma leukemia group of diseases There are numerous reports of familial leukemia as described by J C Cameron (55) Sanger (301) Brugger (50) and others Familial Hodgkin s disease has been reviewed by Arkin (5) who described mediastinal Hodgkin s disease occurring in a father son and nephew The occurrence in twins was reported by Peacocke (269) in a brother and sister and in two brothers by Braun (45)

The only instance of familial mycosis fungoides was described by O J Cameron (56) in a mother and daughter This case had previously been reported by Keim (179a) The 45 year old mother had intermittent severe generalized pruritus for six years associated with an area of redness on the left thigh The entire cutaneous surface was diffusely erythematous and scaly with many poorly defined areas of thickening and many infiltrated areas of various size and shape which tended to be circular dull red and extensively excoriated She had mild superficial lymphadenopathy and hepatosplenomegaly and 7 per cent eosinophils in the peripheral blood The disease followed a typical course and she died nine months after onset She had 14 children only two of whom were living the others having died from intercurrent infections shortly after birth At the time of her death a 22 year old daughter who was apparently in subjective good health developed pruritus Seven years later she presented a marked generalized intermittent pruritus and an oval patch of dermatitis which had been present on the side of the neck for one year This lesion gradually increased to half dollar size and was intensely pruritic The skin had become universally reddened and scaly during the previous few weeks and the pruritus increasingly severe She had superficial lymphadenopathy and splenomegaly

This latter patient was reported by Wile (362c) when she was 34 years of age The disease had progressed slowly until numerous flat semilunar lesions (depigmented areas at sites of previous lesions) had appeared one year before which involuted following roentgenotherapy Autopsy examination de

scribed by Wile and Knerler (362d), disclosed advanced lymphomatous involvement of the periaortic and mediastinal lymph nodes and neoplastic lymphoid infiltration in the mediastinal fat and connective tissue Scattered lymphomatous infiltrates some one cm in diameter were present in the lungs The bronchial and infrapulmonic lymph nodes invading through the capsule into the mediastinum showed lymphomatous transformation There was involvement of the diaphragm and extensive changes in the spleen with involvement of the capsule while the liver showed infiltration in the portal areas Histologic diagnosis of the skin was "lymphoblastoma cutis There was marked lymphoid infiltration about the blood vessels and accessory cutaneous structures in the subpapillary layer of the corium and extensive accumulations of histiocytes containing granules of brown pigment were present in the cutis The cells of the neoplasm were of undifferentiated lymphoid type Some lymph nodes which had undergone extensive lymphomatous transformation showed little destruction of the usual architecture An unusual characteristic of the neoplasm was its association with extensive infiltration of eosinophils and also an extensive infiltration of eosinophils in the bone marrow Wile and Knerler commented that this patient had never had large fungating tumors such as occurred in her mother despite the development of characteristic prefungoid infiltrative plaques from time to time A few small nontender elevations had appeared however on the legs and shoulders but they were never larger than 5 to 7 mms in diameter

Lapowski (198i case 2) reported a 42 year old man with classical mycosis fungoides of 15 years duration whose father had died of leukemia

D Occurrence in the Negro

The largest series of Negro patients having cutaneous diseases was reported by Hazen (148a) who studied 11 729 consecutive cases not including syphilis He found only nine cases of mycosis fungoides in this group which led to the impression that this disease occurred less frequently in Negroes

In a study 12 years later, Hazen (148b) found 14 (0 1 per cent) were Negroes and concluded that, although the disease was somewhat less frequent in Negroes, it was not as uncommon as was formerly believed

The frequency of mycosis fungoides in the white race was reported by Pollitzer (275a, b) to be 0 03 per cent and by Crocker (71a) to be 0 24 per cent

Among 359 patients having dermatological diseases, Sigel (317) found 48 per cent to be Negroes There were seven cases of mycosis fungoides in this group, four of whom were white and three Negro He gave detailed reports of the three Negroes and concluded that the histologic and clinical features of mycosis fungoides were the same in both races He cited a number of dermatologists who believed the disease to be less common in the Negro At the Cook County Hospital in Chicago, where there are more than 45 per cent Negro patients, we have found there is an equal frequency of mycosis fungoides in the Negro and white race

It was also believed, in the past, that Negro women were more frequently affected than Negro men, according to Hazen (148b), while in the white race the incidence is higher in men than in women, as reported by Crocker (71a) This observation appears to be correct for patients having classical mycosis fungoides We noted the following incidence among 39 Negro patients

TABLE V

INCIDENCE IN THE NEGRO RACE

Type	*Men*	*Women*	*Total Cases*
Classical	14	20	34
"D Emblee	4	0	4
"Erythroderma	1	0	1

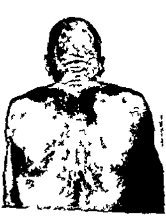
Although there is agreement that the manifestations of mycosis fungoides are the same in both races, there are reports of unusual features in Negroes Strobel and Hazen (326 case 2) described cutaneous lesions resembling erythema multi

forme in one case. Ebert and Slepyan's (93c) patient had purpura and Weidman and Gilman (352b) reported a patient who had leg ulcers. Urticaria occurring either as the primary lesion or during the course of the disease was noted by Wolff (369), Wertheimer (359) and Guy and Amshel (144). Leonine facies were also described by Guy and Amshel and Wertheimer's patient had cutaneous lesions which resembled hypertrophic lichen planus. Definite tumors developed in these areas.

The first report of mycosis fungoides occurring in a Negro was that of Strobel and Hazen (326) in 1911. However, they stated that Bloodgood (36) had previously observed such a case. Since then this occurrence has been described by others including Beerman and Thomas (19), Bell (21), Cross (72), Ebert (95a), Ebert and Otsuka (95b), R. C. Jamieson (170), Kennedy *et al* (180), Lawless (201), Mitchell and Scull (243b, c), Netherton (251), Nicholas (253), Oliver (259c, e), Quero (282), Rattner and Rodin (287) and Weiss (354).

Case Report. A 65 year old Negro first developed fine bumps on the dorsum of the left foot one year previously. This eruption spread to involve the left leg two weeks later





3. Mycosis fungoides in a Negro (case report)
4. Mycosis fungoides in a Negro (case report)

and, the following week, the right foot and leg became similarly involved During the next few months similar lesions appeared on the forearms, arms, trunk and face Although some of the lesions disappeared spontaneously, new lesions appeared The eruption was pruritic, particularly when he was warm One year after onset of these lesions, thick patches" appeared on the left forearm which gradually became generalized There were infiltrated lesions scattered irregularly on the trunk and extremities and near the left ear On examination, he presented a generalized papular eruption, which tended to follow the lines of cleavage, on the back and neck Some of the papules coalesced to form hyperpigmented patches most of which were raised infiltrated and irregularly shaped The lesions were slightly scaly and there was a crusted lesion on the extensor surface of the right arm There was moderate hyperkeratosis of the plantar surfaces of both feet which was most marked at the borders There was fissuring, particularly of the great toes He had moderate cervical and axillary lymphadenopathy The hemogram revealed 5,900 white blood cells per cu mm, with 64 per cent polymorphonuclears 12 per cent lymphocytes, 13 per cent band forms 10 per cent monocytes and 1 per cent eosinophils Histologic examination of a cutaneous lesion showed mycosis fungoides

Other examples of mycosis fungoides in Negroes are illustrated

E. Trauma

Most cases of mycosis fungoides in which trauma is mentioned as an important factor are of the "d emblee' type and in my opinion, are instances of lymphosarcoma These initial cutaneous patches of mycosis fungoides are probably the primary lesions which Hallopeau and Leredde (145j) called the chancre of the disease" and are frequently misdiagnosed Audry (10) believed that early excision of a solitary tumor would be curative

The development of mycosis fungoides following an insect bite was reported by Eller and Rein (98b) who stated that the bite may possibly have been merely coincidental The patient

described by Howles and Connell (158) developed an acute exacerbation of cutaneous lesions following a hordeolum

Riecke (292) reported a 35 year old man who developed mycosis fungoides "d'emblee" following an injury Goeckerman and Montgomery (132) described a 62 year old woman who had injured her knee three years previously There was



5 Mycosis fungoides in a Negro

no permanent discomfort from this injury but following another injury to this same area 18 months later she developed an irregularly outlined ulcer in the left tibial region which proved to be mycosis fungoides Crocker (71c) reported a patient who developed prolonged suppuration in the head of the tibia and lymphangitis following a knee injury One year later mycosis fungoides appeared

Owen-Jones (264) described a patient who developed cellulitis at the site of a drainage wound the second week after surgery for a perforated duodenal ulcer. This lesion gradually spread to resemble an ulcerated granuloma but the laparotomy



6 Mycosis fungoides in a Negro

wound was not involved Histologic examination revealed mycosis fungoides and death occurred ten months later The patient reported by Behaegel (20) developed what was believed to be a solar dermatitis which had reappeared on exposed





7 Mycosis fungoides in a Negro
8 Mycosis fungoides in a Negro

cutaneous areas for five successive summers An infiltrated lesion then appeared on the face which proved to be mycosis fungoides The final diagnosis was "premycotic urticarial dermatitis provoked by sunlight"

It would appear that trauma is an important factor only in the "d emblee" type of the disease and is not of major consequence in classical mycosis fungoides

F. Sites of Involvement

There are several studies on the predominant sites of involvement in mycosis fungoides. In a series of 13 cases Poulsen (278) found six patients had localization in the scapular region (one on the left and five on the right side) while the face, trunk, and proximal areas of the extremities were the next in frequency. Gates (125) reported 45 cases of mycosis fungoides having the following sites of involvement:

Site of First Cutaneous Tumor				*Regions Involved*			
Head	*Trunk*	*Entire Body*	*Extremities*	*Head*	*Entire Trunk*	*Body*	*Extremities*
4	7	1	6	14	19	14	22

Among 214 cases studied by Heite and Socha (150), the sites of involvement were found to be:

Localization	*Men*	*Women*	*No Sex Given*	*Total*
Entire body	25	17	3	45
One site	77	63	12	152
More than one site	9	8	0	17

Of these cases, the specific site of involvement was listed in 152.

Localization	*Men*	*Per Cent*	*Women*	*Per Cent*	*No Sex Given*	*Total*
Head and Neck						
Head	2	2.8	4	6.8	1	7
Neck	15	21	17	29	5	37
Chest	4	5.6	4	6.8	1	9
Trunk						
Abdomen	3	4.2	6	10	0	9
Upper back	6	8.5	4	6.8	2	12
Lower back and nates	7	9.9	4	6.8	0	11
Groin, genitalia and anus	5	7.1	0	0	0	5
No details given	6		4		0	10
Extremities						
Upper	11	15.5	5	8.4	0	16
Lower	18	25.4	15	25.4	3	36

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. . . the following

TABLE VI

SITES OF PRIMARY INVOLVEMENT

Site of Involvement	*Classical*	*"D'Emblee"*	*"Erythroderma"*
Head and neck	28	27	5
Upper extremities	51	14	2
Lower extremities	85	18	6
Trunk	93	21	3
Crural genital region	5	5	1
More than one site	55	4	18

G. Experimental Observations

Several investigators have reported the apparently successful transmission of mycosis fungoides to rabbits and guinea pigs but on the whole these results have not proved to be entirely convincing

In 98 experiments, Zurhelle (378) was able to produce tumors suggestive of mycosis fungoides in two guinea pigs Further passages from the animals frequently, but not invariably, produced pathological changes and death, although the findings were not typical of mycosis fungoides In two instances, pure cultures of a small gram negative bacillus were obtained which produced fairly constantly, local infiltrations and ultimately pulmonary, hepatic and splenic nodules in guinea pigs Although these results concurred with the findings of Bodin and Chevrel (40), Zurhelle stressed the fact that they were inconclusive since, in no instance, was true mycosis fungoides produced

Bruniuer (51a b) described the results of subcutaneous injections into guinea pigs of diseased splenic tissue from a patient having mycosis fungoides The inoculated animals developed nodules identical to those present in the patient, in the liver spleen and inner side of the sternum, nine weeks after the injection

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Neck	15	21	17	29	5	37
Chest	4	5 6	4	6 8	1	9
Trunk						
Abdomen	3	4 2	6	10	0	9
Upper back	6	8 5	4	6 8	2	12
Lower back and nates	7	9 9	4	6 8	0	11
Groin genitalia and anus	5	7 1	0	0	0	5
No details given	6		4		0	10
Extremities						
Upper	11	15 5	5	8 4	0	16
Lower	18	25 4	15	25 4	3	36

and these reactions in mice it would favor a toxic or virus etiology in mycosis fungoides rather than a malignant cell tumor

H Occurrence in Animals

Wirth and Baumann (367) described multiple cutaneous nodules and internal organ involvement in a dog These lesions composed of pleomorphic granulation tissue were identical to those present in human beings with mycosis fungoides Hofstra (157) reported cutaneous tumors affecting two cows The first animal was given acetanilid internally which resulted in healing four weeks later but no histologic studies were done The second animal was given potassium iodide internally but did not improve and having become cachectic was killed three weeks later A diagnosis of mycosis fungoides was established by histologic examination

I Lymphodermia Perniciosa

Lymphodermia perniciosa was first described and named by Kaposi (176a) in 1885 He described a 39 year old man who had a partly diffused partly localized scaling moist intensely pruritic eczema of six months duration Diffuse soft swelling and thickening of the affected areas gradually appeared followed by cutaneous and subcutaneous nodules which were in part ulcerated There was lymphadenopathy splenomegaly and pallor while "shapeless nodular thickenings" involved the face ears forehead lips thorax and arms An absolute increase of the peripheral white blood cells (125 000 per cu mm) occurred and the leukemia caused death Autopsy revealed the spleen to be four times normal size and the sternal vertebral metatarsal and long bone marrow were grayish in color "from the excess of white blood cells Leukemic nodules were found in the pleura lungs and cutis Because of the tumor formation Sequeira and Panton (311c) considered this case to be mycosis fungoides

Paltauf (265b) regarded this condition to be a variety of mycosis fungoides with generalized dermatitis and subcutane

Experimental observations were conducted over a period of nine years by Stratton (325a). He described a 50 year old woman who had an intensely pruritic, polymorphous cutaneous eruption. These crescentic lesions, which resembled erythema multiforme, plaque like lesions and psoriasiform lesions, were present for seven years before the development of tumors. She died two years after the tumors appeared and autopsy revealed generalized cutaneous mycosis fungoides and cutaneous infiltration of the breast and kidneys. Experimental studies consisted of grafting one portion of a nonulcerated cutaneous nodule under the skin of four mice and two guinea pigs. All results were negative. The other portion was emulsified with saline solution and inoculated into tubes containing brain broth and Sabouraud's solution, but none yielded growth. Blood plate inoculation resulted in a growth of bacillus proteus and bacillus coli within 24 hours. This emulsion was then injected intraperitoneally into three mice and intracerebrally into three others. Ten months later, two mice (one injected intraperitoneally, one intracerebrally) showed evidence of leukemic infiltration of some organs, particularly the liver and spleen. Mouse to mouse transfer, for three passages, was done for a three year period and chorio allantoic membranes were inoculated.

The results of similar transfers of tissue from three other patients was later reported by Stratton (325b). Transfer was done in the first case at an advanced stage of the disease shortly before the patient's death. He stated that all animal inoculations were negative at the time of the report. In the second case, an emulsion of the tissue was injected into the brain of six mice and into the peritoneal cavity of another six. Thirteen months later, one brain injected mouse died and the liver was found to be five times normal size while the spleen was 20 times the normal size. Histologically, these organs revealed infiltrations similar to those present in mycosis fungoides as noted in his previous studies (325a). Stratton concluded that in view of the reactions produced in three out of four cases should a correlation exist between human mycosis fungoides

V

PATHOGENESIS

THE PATHOGENESIS of mycosis fungoides appears to be one of the most perplexing problems in medicine Its nosologic status is far from settled and there is no complete agreement as to the proper name for the condition The present classification of mycosis fungoides as one of the lymphomas places it in a group consisting of vague manifestations of reticuloendothelial system disease not readily classifiable Another confusing aspect is whether or not mycosis fungoides should be considered as a disease sui generis or merely as a clinical manifestation of leukemia Hodgkins disease or lymphosarcoma

The source of confusion probably lies in the improper classification of cases namely the inclusion of mycosis fungoides d emblee" (Vidal and Brocq 346c) and the "erythroderma (Hallopeau 145a) types of mycosis fungoides with the classical (Alibert) form of mycosis fungoides In my opinion (38b) the d emblee" type is nearly always lymphosarcoma except in very rare cases in which it is the primary lesion of Hodgkins disease (chancre lymphogranulomateaux) while the "erythroderma form is a manifestation of either lymphocytic leukemia Hodgkins disease or lymphosarcoma The classical form described by Alibert is the only form which constitutes true mycosis fungoides This supposition is in disagreement with Symmers (331c) theory that mycosis fungoides is a clinical and pathologic non-existent I favor Robb Smiths (293) opinion that "Through all the varying accounts one gains the impression there is a distinct clinical entity with a characteristic histology and that if really critical observation and histology were applied to these disorders (reticuloses) mycosis fungoides

ous tumors and believed it to be related to mycosis fungoides rather than identical with leukemia cutis. This opinion was concurred by Arzt (7a). Lymphodermia perniciosa is listed as a synonym of mycosis fungoides in Stelwagon's (321) text book.

The present consensus is that Kaposi's original case was one of leukemia cutis associated with chronic lymphocytic leukemia and not mycosis fungoides. It is interesting that with modern hematological diagnostic methods, lymphodermia perniciosa is never considered in a diagnosis. The term lymphodermia perniciosa is no longer included in dermatological literature.

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The acceptance of mycosis fungoides as a specific disease

The histologic picture is specific, according to Jaffé (168), who described the cutaneous changes in the cutis as infiltrations of great cellular polymorphism and very rich in eosinophilic leukocytes. He found large, round cells with a delicate cytoplasm and round, oval or irregularly shaped nuclei showing a distinct chromatin net, to be present in all three stages but most marked in the tumor stage. There were also giant cells, often with a vacuolated cytoplasm and up to twenty nuclei. He believed the most characteristic elements to be the large cells with delicate cytoplasm which form the bulk of cells in the tumor-like nodes.

The large mycosis cells, as described by Jaffé (168), are very vulnerable, the cytoplasm melting down "as if it would be washed away, while the nuclei shrink, become pyknotic and assume bizarre shapes." This great vulnerability of the cells, he stated, explains the often rapid spontaneous regression of the lesions. When the nodes break through the epidermis and become ulcerated, secondary infections may obscure the characteristic picture.

The mycosis cells originate locally, according to Jaffe (168), and since they frequently occur about blood vessels in the earlier stages, a genetic relationship to adventitial and periadventitial histiocytes has often been considered. In his opinion although the majority of large cells develop from local histiocytes, fibrocytes may also undergo a similar transformation.

The striking histologic features of typical mycosis fungoides were described by Highman (156b) as distinct epidermal changes similar to those present in chronic eczema, namely, vesiculation, spongiosis, hyperkeratosis, parakeratosis and acanthosis. He described the most significant findings, present in the papillary body and upper layers of the corium in the form of an infiltration which, if typical, left no doubt as to the

would stand out even more certainly as a disease with a characteristic natural history and pathology

A Nosology

L McCarthy (224a) aptly said that "Mycosis fungoides passes through so many different stages and shows so many phases of each stage that it is not surprising that it may simulate very closely a large group of diseases at one time or another"

A better understanding of the various etiological interpretations of *mycosis fungoides* may be found in reviewing some of the pertinent literature Although mycosis fungoides is a comparatively rare disease it has nevertheless resulted in diverse opinions regarding its exact nosologic status which according to Fraser (114a), can be explained by one of nine following views

1) Granuloma (Auspitz 11 Kobner 187a b MacLeod 229 Ormsby and Montgomery 261d Stelwagon 321)

2) Cutaneous form of lymphadenoma (Gillot 128 Ranvier 286)

3) Lymphosarcoma (Fraser 114b c Hemmingson 152 Keim 179a Mayr 236a b Paltauf 265a Sredey 318)

4) A condition half way between granuloma and sarcoma (Radaeli 285)

5) A lymphemic or aleukemic lymphomatosis (Pardee and Zeit 266)

6) Sarcoma engrafted on previous dermatoses such as psoriasis or eczema (Kaposi 176c)

7) Last phase of a series of dermatoses such as pityriasis rosea and parapsoriasis (Brocq 48b)

8) Lymphoma of the skin (Strobel and Hazen 326)

9) Cutaneous manifestation of systemic disease of toxic origin such as Hodgkin's disease or lymphosarcoma (Gates 125 Symmers 331a Gadrat 118)

To this list may be added

10) Reticuloendothelial system disease (Berger and Vallee 26 Cottini 69 Grynfeltt *et al* 143 Herzberg and Ueberschar 155 Jaffe 168 Zoon 376)

dependent on the type of leukemic cells present they are usually lymphocytes or more rarely granulocytes This infiltration is deeper than in mycosis fungoides it is found in perivascular foci related to the position of the lymphatic spaces and appears as a continuous sheet if the foci are fused while the papillary and subpapillary layers are not usually involved Two hypotheses to explain the presence of the cells have been advanced migration from the blood stream or local development from the reticuloendothelial system The epidermal changes are those of the dermatoses simulated although there are no significant changes in nodules or tumors other than mechanical stretching or narrowing The important histologic characteristics of leukemia cutis are the depth of the infiltration and the true lymphocytic or granulocytic type of cell The site of the infiltration as well as the epidermal changes in Hodgkin s disease are essentially the same as those of leukemia However the infiltrations are strongly suggestive of a lymph node and when Sternberg Reed cells are also present the microscopic picture is characteristic Cutaneous lesions of lymphosarcoma show the history of lymphosarcoma and resemble no other condition

Symmers (331c) expressed the opinion that mycosis fungoides is a nonexistent disease a view supported by Berman (29) and many pathologists Why has this view been accepted generally by most pathologists and some dermatologists? It is primarily due to the fact that dermatologists have misled the pathologist The current dermatologic conception is that mycosis fungoides may begin in one of three forms 1) the classical type which undergoes three typical stages namely the premycotic infiltrative and tumor stages 2) the "erythroderma type and 3) mycosis fungoides "d emblee" In our opinion it is more practical to eliminate those cases designated as "erythroderma or "d emblee" at the onset and confine one s conception of mycosis fungoides to the classical type rather than to describe the disease as "nonexistent" The d emblee" form is nearly always a manifestation of lymphosarcoma it is lymphosarcoma from inception to termination and occasionally

diagnosis However, it is not always typical and "Herein lies the kernel of the problem as to the inter-relationship of the lymphodermas" When this infiltration is characteristic, it in no way suggests leukemia, Hodgkin's disease, or any other related condition, nor does it resemble any variety of sarcoma It consists of a great variety of cells elongated, circular, some with deep staining nuclei, others paler, lymphocytes, often plasma cells, many mitotic figures, and a peculiar multinucleated cell A slight degree of variation is found at different stages of the lesions Mitosis is more evident during the period of development At the height of development, there is a slight degree of cellular destruction, which accounts for the temporary stabilization of the fully matured lesions During the period of involution there is a progressively increasing amount of cell granulation and detritus with a decrease, to the vanishing point, in karyokinesis A microscopic diagnosis is not possible during the final stage but can always be made in the first two stages If these features are not present after repeated examination of several lesions from different areas at different stages of growth and decline, the disease is not mycosis fungoides even though the clinical diagnosis may be mycosis fungoides, according to Highman His description of *the histology of mycosis fungoides applies equally well to the* prefungoid (premycotic) and fungoid stages, the inference is that no prefungoid stage exists when strictly interpreted, except as a clinical picture He emphasized that from the onset mycosis fungoides is always mycosis fungoides histogenetically, although the histologic picture cannot be recognized at the inception because the characteristic anatomic features of the disease have not asserted themselves at that stage Therefore the diagnosis of mycosis fungoides cannot always be made microscopically or grossly and in these cases only constant observation will lead to the correct diagnosis

In describing the differences between mycosis fungoides leukemia cutis, Hodgkin's disease and lymphosarcoma, on a histological basis, Highman (156b) gave the essential points of diagnosis The characteristic infiltration in leukemia cutis is

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it may be the primary lesion of Hodgkin's disease (chancre lymphogranulomateux) The erythroderma form may on the other hand be either a clinical manifestation of Hodgkin's disease chronic lymphocytic leukemia or lymphosarcoma There are no substantiated reports of cases having the clinical picture of erythroderma or the d'emblee type showing post mortem findings of mycosis fungoides Neither of these forms should be considered mycosis fungoides only the classical (Alibert) type should be considered true mycosis fungoides In further evaluating this theory let us examine the following "d'emblee cases

In 1885 Vidal and Brocq (346c) described a patient having cutaneous tumors which began as nodules Although the disease manifested *neither a premycotic nor an infiltrative* stage it was called mycosis fungoides d'emblee despite the fact that Siredey (318) pathologist at the Paris Hospital reported it to be histologically lymphosarcoma

In attempting to interpret mycosis fungoides as a variety of lymphosarcoma Fraser (114b) described a woman who developed swelling and a nodular mass on the ankle following injury He commented that this was a case which in its clinical aspects throughout its whole course was a straight forward mycosis fungoides and was so diagnosed by several competent dermatologists In its mode of onset with tumor formation and the absence of any history of a so called premycotic dermatoses we have a perfect picture of that variety of the disease first described by Vidal and Brocq as mycosis fungoides tumeurs d'emblee His second case report is too vague for evaluation but since there was no premycotic stage preceding the tumor development it would probably be classed with the d'emblee type The third patient developed a circular ulcerative lesion on the wrist following trauma a clinical picture of the d'emblee type but histologically lymphosarcoma

Unilateral involvement limited to one or a few tumors occurring in the d'emblee form appears to be a more highly malignant type of lymphosarcoma than the so called inverse type in which tumors are followed by erythematous and in

filtrated lesions There are reports of unilateral involvement in a patient having the primary lesion of the testis following [illegible] (Spencer 310)

In our opinion all erythroderma" cases are either leukemia Hodgkin s disease or lymphosarcoma from the onset We have been unable to find any authentic report of the "erythro derma" type of mycosis fungoides which did not prove to be chronic lymphocytic leukemia Hodgkin s disease or lymphosarcoma on postmortem examination

Symmers (331c) described a patient with exfoliative derma titis and a white blood cell count of 164 000 per cu mm as a case of "mycosis fungoides " although this patient had lympho cytic leukemic erythroderma The most frequent cutaneous manifestation of the so called "lymphoblastomas" is a persistent scaling erythroderma according to Wile (362b) Two of his patients having erythroderma had chronic lymphocytic leu kemia one had Hodgkin s disease and one lymphosarcoma Two patients in Gates (125) series had exfoliative dermatitis and although the clinical diagnosis was mycosis fungoides histological examination showed scirrhous Hodgkin s disease A patient with clinical exfoliative dermatitis found to have Hodgkin s disease at autopsy was reported by Montgomery (245a)

Although the French dermatologist Alibert was the first to describe mycosis fungoides it would appear that his com patriots Vidal and Brocq and Hallopeau have confused the subject by including the "d emblee" and erythroderma forms with mycosis fungoides

B Relationship of Mycosis Fungoides to Other Diseases of the Leukemia Lymphoma Group

Hodgkin s Disease A relationship between mycosis fung oides and Hodgkin s disease was suggested as early as 1872 by

Ranvier (286) Ziegler (374) also expressed the opinion that *mycosis fungoides* was a cutaneous form of Hodgkin's disease, a relationship perpetuated by others (Berger and Vallée 26, Bowen 43, Chevallier and Bernard. 62, Paltauf 265c, Strobel and Hazen 326, Wechselmann 351). It cannot be denied that in certain cases having both cutaneous and internal organ involvement either diagnosis would be justified, as pointed out by Goldsmith (136b). However, this fact seems to prove the limitations of the means of diagnosis rather than the identity of the two diseases, according to Wertheim and Smith (358) This resemblance is evident, however, because the parent tissue of the two diseases is the reticuloendothelial system

Through the work of Arndt (6b) and Arzt (7b), these two diseases were separated and classified as distinct entities Although a clinical and pathological similarity exists between these two diseases, as evidenced by the comparative tables of Strobel and Hazen (326), mycosis fungoides involves primarily the reticuloendothelial system of the skin, while Hodgkin's disease affects primarily the lymph nodes In classical mycosis fungoides, eczematoid, sharply defined erythematous lesions having the histology of the disease are an early symptom and precede the tumor formation The difficulty in clinical and histological differentiation of these two diseases was illustrated by Fraser (114a) who concluded they were different diseases caused by agents which under certain conditions, could stimulate the tissues to very similar reactions

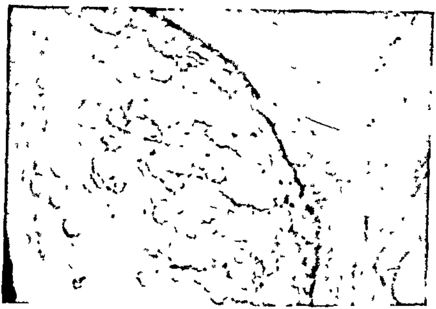
An important diagnostic point appears to be the age of the patient Mycosis fungoides occurring under the age of 10 years was reported only once in a patient described by Serra *et al* (313) and only about a dozen cases occurring under the age of 20 years could be found in the literature Numerous reports of Hodgkin's disease affecting children can be found in the literature Most cases of mycosis fungoides occurring in children were of the "d'emblee" type and, therefore, were probably lymphosarcoma or Hodgkin's disease

Mycosis fungoides invariably affects the skin Regional or generalized lymphadenopathy, with or without specific histo-

logic changes occurs in many cases whereas Hodgkin's disease affects primarily the reticulum of the hematopoietic organs namely the lymph nodes spleen and liver Cutaneous lesions of Hodgkin's disease are classified as specific (infiltrations nodules and ulcers) and nonspecific or toxic (generalized pruritus with or without lichenification and pigmentation papular vesicular and urticarial eruptions purpura herpes zoster and exfoliative dermatitis or generalized erythroderma) The cutaneous lesions of the nonspecific type present no characteristic appearance and the order of their appearance does not suggest a subdivision into different stages The histologic picture of the nonspecific lesions is not diagnostic since there is usually no typical infiltration The correct diagnosis can be made only by study of the history clinical manifestations and histologic examination of the lymph nodes and involved skin The blood picture is usually normal however an eosinophilia of more than 10 per cent is usually more suggestive of mycosis fungoides although eosinophilia is not a constant feature of this disease In many cases of mycosis fungoides eosinophils were not found although counts as high as 95 per cent were recorded by Wills and Hadfield (363c)

We observed one patient who had ulcerated cutaneous nodules which were reported to be mycosis fungoides on histologic examination The diagnosis at autopsy however was Hodgkin's disease The cutaneous serial sections were then reexamined and two slides revealed Sternberg Reed cells characteristic of Hodgkin's disease

A 24 year old man reported by Wile and Stiles (362e) had a generalized pruritic eruption numerous excoriated papules and linear lesions as well as nodules and plaques Histological examination of a lymph node revealed Hodgkin's disease Is it not possible that this patient did not have mycosis fungoides at any time and that the condition was Hodgkin's disease from the onset? Scratched papular and linear excoriations are a frequent toxic manifestation of Hodgkin's disease whereas excoriated lesions are seldom present in mycosis fungoides in spite of the intense pruritus



9 Ulcerated nodules of mycosis fungoides (Bluefarb and Schwartz Arch Dermat, Feb 1956)

Three cases of scirrhous Hodgkin's disease, clinically diagnosed as mycosis fungoides, were reported in Gates' (125) series In a review of these cases it is apparent that the first two patients had exfoliative dermatitis, and the disease should not have been considered as mycosis fungoides since, in our opinion, exfoliative dermatitis does not occur in this disease The third patient in this series had specific cutaneous Hodgkin's disease, the histology of the cutaneous tumor and the lymph nodes revealed scirrhous Hodgkin's disease

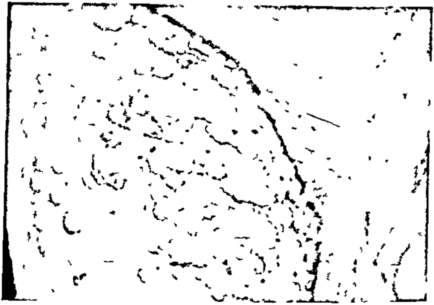
A close relationship between leukemia, Hodgkin's disease and mycosis fungoides was illustrated in Montgomery's (245a) patient who had exfoliative dermatitis The white blood cell count was 20,000 per cu mm, with 60 per cent lymphocytes, and a diagnosis of leukemia was made although histologic examination of a lymph node revealed typical Hodgkin's disease The cutaneous lesions had undergone involution and no lesions appeared for a period of two years when numerous discrete plaques, presenting many clinical features of mycosis fungoides

developed Although the cutaneous manifestations were those of exfoliative dermatitis the diagnosis of Hodgkin s disease was confirmed at autopsy

A case of Hodgkin s disease with erythroderma reported by Dujardin and Van der Meiren (92) had been previously diag nosed as mycosis fungoides The skin was pruritic with areas of lichenified eczema on the erythroderma with sclerotic pig mented areas resulting from roentgenotherapy This diffuse cutaneous infiltration preceded the lymphadenopathy and histologic examination of an inguinal lymph node revealed Hodgkin s disease while the cutaneous picture simulated mycosis fungoides

"Two cases of mycosis fungoides indistinguishable from Hodgkin s disease" were reported by Goldsmith (136b) The first patient was a 79 year old man whose only cutaneous lesions were tumors clinically characteristic of mycosis fung oides "d emblee" At autopsy the skin heart liver pancreas kidneys adrenal glands bones and spleen were found to be involved On histologic examination all infiltrated areas ap peared uniform in the organs studied Reticulum cells were the most numerous and mitotic figures were present The second patient was a 48 year old man whose skin had always been dry and pronounced scaling had been present for the preceding 12 years There was universal redness scaliness thickening and looseness of the skin in some areas A raised purple lesion 7 6 by 2 5 cms was present on one forearm and a few oval tumors were present on other parts of the body Clinically this case conformed to the "erythroderma" type of Hallopeau and Besnier but histologically there was also a marked uniformity in the infiltrated areas although the cell types were more numerous Reticulum cells with large nuclei predominated but were usually larger than those found in the first case There were also numerous larger cells some with a single nucleus but the majority were typical of Sternberg Reed cells

In a comparative study of mycosis fungoides and Hodgkin s disease Lapiere (197b) concluded that the two diseases were



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kemic lymphomas of the lungs skin liver spleen and intestines In our opinion this patient might well have had both specific and nonspecific cutaneous lesions of leukemia but not mycosis fungoides

A 42 year old man reported by Fraser (114c), had an eczematoid dermatitis which was followed by infiltrated erythematous plaques in the dermis Two years later lymphadenopathy and generalized ulcerating cutaneous and subcutaneous nodules appeared and shortly before death splenomegaly and a lymphocytic leukemic blood picture developed

Berman's (29) patient was a 57 year old woman who had a red scaly pruritic cutaneous eruption of five years duration which first appeared under the left breast but gradually spread to involve the anterior part of the thorax upper and lower extremities and the face At autopsy the skin was dry smooth shiny and of a universal brown color with some scaling The scalp and eyebrow hair was almost entirely absent but there was no loss of hair in the axillary or pubic regions A widely distributed eruption of reddish purple macules from 1 mm to 1 cm in size was most marked on the upper thorax while a deep sharply defined ulcer 11 by 7 cms in size having a dry base was present on the left breast There was discrete lymphadenopathy involving the axillary cervical and inguinal nodes Bone marrow imprints showed granulocytes in various stages of development in abundance of lymphocytes and occasional immature lymphocytes of reticular origin similar to those present in the skin This diffuse macular eruption was similar to that seen in some forms of leukemia according to Berman The pathologic diagnosis in this case was leukemic reticuloendotheliosis

The leukemias are essentially different from mycosis fungoides in that leukemic processes always remain a proliferation of leukocytes while the lesions of mycosis fungoides may eventually resemble "granulation tissue" as emphasized by Paltauf and Zumbusch (265c) No better summary to this question can be found than the simple facts so well set forth by Highman (156a b) He said that a disease resembling

separate entities and that neither develops into the other. In my opinion Hodgkin's disease and mycosis fungoides are different diseases which are, in all probability, caused by similar agents which, under certain conditions, can stimulate the tissues to similar clinical reactions.

A patient having pruriginous, eczematous cutaneous plaques on the lower extremities was presented by Milian (241a). The clinical diagnosis was mycosis fungoides. Cervical lymphadenopathy and cutaneous lesions of Hodgkin's disease then appeared and the patient died. On histologic examination at autopsy, the cutaneous lesions showed hypertrophic endothelial cells of the capillaries, connective tissue cells with extremely large nuclei and many lymphocytes. This picture was regarded as characteristic of mycosis fungoides until examination of the typical Hodgkin's lesions in the cervical lymph nodes indicated the two lesions were probably the same. Milian mentioned another patient who had the same type of cutaneous lesions. He stated that he was convinced that these two diseases are morphologically inseparable until the causative agents of the diseases is known. However, in discussing these cases Cailliau (54) expressed a different opinion. He believed that the cutaneous lesions in these two diseases are alike in only one respect, the response of the histiocytes, while the giant cells, infiltration, sclerosis and macrophages are alike in no respect.

Leukemia. Cutaneous tumors clinically indistinguishable from those present in mycosis fungoides have been described in many cases of leukemia cutis. The classic example of lymphodermia perniciosa reported by Kaposi (176a), in a patient with chronic lymphocytic leukemia, was misdiagnosed as mycosis fungoides by many investigators (see Lymphodermia Perniciosa).

The first report of this association was made by Pardee and Zeit (266). The anatomical diagnoses in their case were lymphocytic leukemia with marked hyperplasia of the spleen and the cervical, axillary, inguinal, mediastinal, bronchial, celiac, mesenteric and retroperitoneal lymph nodes and leu-

of mycosis fungoides described by Bowen (43) appears to indicate the condition was sarcoma since pathologists did not distinguish between round cell and lymphosarcoma at the time of his report The primary growth in one patient occurred in the testis following injury The distribution and character of the cells which were described as being present in the "lower part of the corium" and composed mainly of "numerous small round cells" would indicate a sarcoma

Round cell sarcoma of fibroblastic origin is rare, according to Fraser (114b) who considered the cases described by Gottheil (138) and Breakey (47) as probable examples of lymphosarcoma Breakey's case was reported as one of mycosis fungoides but autopsy revealed sarcomatosis (lymphosarcoma or small round cell sarcoma) of the skin with secondary growths in the tonsils lungs and the cervical axillary and cubital lymph nodes

Again this confusion exists because the "d emblee" type was not separated from the classical form of mycosis fungoides The "d emblee" form is practically always lymphosarcoma from its inception whereas the classical form is not lymphosarcoma although there may occasionally be a close histopathological resemblance





10 Mycosis fungoides "d emblee"
11 Close up of illustration 10

mycosis fungoides, but having the blood findings of leukemia is never *mycosis fungoides but is leukemia. A disease resembling* mycosis fungoides, but having the histologic lymph node changes of Hodgkin's disease is not mycosis fungoides but Hodgkin's disease. This same reasoning also applies to lymphosarcoma. One must also consider a possibility mentioned by Robb-Smith (293), namely, that the leukemic blood picture in reticulum cell diseases is an epiphenomenon.

Lymphosarcoma. Many investigators, including Ewing (100) and Fraser (114c), have considered mycosis fungoides to be a reticulum cell lymphosarcoma. From a purely clinical standpoint, Fraser (114b) reported his case as mycosis fungoides, as it is described in dermatological literature, but on a pathological basis, this case should be classified as lymphosarcoma. Careful histologic study of cutaneous lesions in both the early and late stages were made in this case, and the picture of the lesions, barely visible grossly, was identical with that of the fully developed tumors. The majority of the cells *were of a uniform type, of round or spheroidal shape,* and three to four times as large as normal lymphocytes. The picture was that of a new growth from the start, according to Fraser.

Robb Smith (293) pointed out that although an infrequent case of mycosis fungoides may become reticulosarcoma, this does not prove the primary neoplastic nature of mycosis fungoides. He stated that it may be difficult to "distinguish between a progressive hyperplastic condition and a blastoma. Though it is uncommon, many reticuloses do undergo sarcomatous changes and there is no reason why mycosis fungoides should not occasionally undergo such a change."

Mycosis fungoides with the histopathologic picture of round cell sarcoma was described in Ormsby and Montgomery's (261d) textbook. A similar case reported by Gottheil (138), was mycosis fungoides clinically, but at autopsy all the organs were found to be studded with lesions which were histologically round cell sarcoma.

The clinical history and course of the disease in two cases

the different aspects of mycosis fungoides acts selectively on the reticuloendothelial system and is capable of provoking the diffuse and generalized picture of the systemic form, as well as circumscribed localized manifestations, has gained increasing support

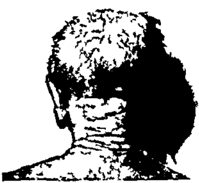
Flarer (107) concluded that mycosis fungoides, whether inflammatory or neoplastic, is a disease of the reticuloendothelial system probably including that of the internal organs and bones He believed the cutaneous and blood changes to be secondary, and some evidence of systemic hyperplasia of the reticuloendothelial tissue must be present if a diagnosis of mycosis fungoides is to be made On the other hand, the majority of investigators, including Thomson (332b), are of the opinion that the primary and specific involvement occurs in the reticuloendothelial tissue of the dermis, while visceral involvement is secondary and less severe

Many investigators agree that there is a close relationship between various lymphomatous diseases and certain allied dermatoses (Keim 179a, Wile 362b, Montgomery 245a, Wile and Stiles 362e, Montgomery and Burkhart 245d, Baldridge and Awe 12, Mallory 232, Loveman 219, Warthin 349b) Until the time when there is conclusive proof of a neoplastic benign, inflammatory or infectious etiology of these diseases it is important to differentiate the conditions whenever possible A rational system of classification of mycosis fungoides depends upon the discovery of the etiologic factors

D Infectious Granuloma versus Neoplasm

The pathologic nature of the disease is another major question encountered in reviewing mycosis fungoides There is considerable disagreement as to whether mycosis fungoides should be considered an infectious granuloma or a malignant neoplasm There are three theories concerning the nature of these lesions 1) inflammatory in their essential nature from beginning to end, 2) inflammatory from early stages and later





12 Patient (illustration 10) following roentgenotherapy
13 Patient (illustration 10) following roentgenotherapy

Case Report A 48 year old Negro had nodular cutaneous lesions on the face of 30 months duration These lesions enlarged became pruritic and had spread to involve the entire cutaneous surface during the previous six months The tumor masses on the face appeared necrotic and ulcerated while the large indurated plaques and nodules on the trunk showed erythematous purple discoloration He had generalized lymphadenopathy and splenomegaly Histologic examination of a cutaneous nodule and a lymph node revealed lymphosarcoma

C The Reticuloendothelial System

The generally accepted theory at the present time is that mycosis fungoides is a disease of the reticuloendothelial system The hematologic observations in three cases of mycosis fungoides were described by Cottini (69) from studies of the skin peripheral blood sternal bone marrow and imprints of lymph nodes and cutaneous tumors Reticulohistiocytic cells (Ferrata s terminology) were demonstrated in the blood and in lymph node and skin tumor imprints with the May Grunwald Giemsa staining technic Cottini therefore considered mycosis fungoides as a disease of the reticuloendothelial system and presented convincing photographic evidence of the imprints His theory that the unknown factor responsible for

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transformed into a neoplastic process, and 3) the lesions are neoplastic from beginning to end

The appearance of granulomatous cutaneous lesions during the course of the disease led Unna (344), Ormsby *et al* (261c), MacLeod (229) and others to believe the possible etiologic agent to be infectious However, extensive bacteriologic studies by Herbert Fox (111) failed to demonstrate a definite etiologic organism although experimental work in animal passage of the disease, done by Stratton (325a, b), indicate that the infectious theory should not be discounted This infectious theory was formerly accepted by most observers but in recent years the neoplastic etiology is more generally accepted However, at the present time many are returning to the infectious theory and Werth (357) believed the infiltrating agent to be of the virus group A cytotropic virus with an affinity for the mesenchyme, is mentioned by Paltauf and Zumbusch (265e) as a possible causative agent

Several theories regarding the pathogenesis are mentioned by Niethammer (255) who, in reviewing the literature, found the majority of investigators regarded the process as infectious He obtained a strain of streptococci, partly in pure culture from mycosis fungoides The antigens produced with these strains gave positive complement fixation with two serums from mycosis fungoides These strains failed to show demonstrable pathogenicity in either rabbits or guinea pigs, however, pointing to no definite etiologic significance in this disease An apparently successful attempt was made by Zurhelle (378) to reproduce this disease experimentally in rabbits and guinea pigs However he later found these results were vitiated by the presence of either *Bacterium parathyphosum B*" or 'Corynebacterium pseudotuberculosis" both of which were found to cause similar changes in different animals

The long duration of five to 20 years, or even 40 years, does not indicate a malignant origin of mycosis fungoides, according to Montgomery (245c) This is also true in some cases of Hodgkin's disease and he believed that many cases of lymphoma particularly mycosis fungoides and possibly cu

taneous Hodgkins disease may begin as a benign inflammatory process and as a result of chronic irritation eventuate in a true malignant disease only after a period of months or years This is comparable to the transitions of benign epithelial neoplasms and precancerous dermatoses into malignant epitheliomas as reported by Montgomery (245b)

It should be borne in mind that malignant tumors do not necessarily exclude an infectious etiology It is known that certain tumors in animals such as bird sarcoma and rabbit papillomas have proved to be of infectious origin

It was pointed out by Montgomery and Burkhart (245d) that any chronic dermatosis or benign inflammatory process which develops as a result of chronic irritation may eventuate in malignant lymphoma after months or years and this fact was reemphasized by Bluefarb and Webster (38g) It was demonstrated by Fischer Wasels (106) that a benign or infectious process may through chronic irritation eventuate in epithelioma while other examples of this change are chronic leg ulcers leukoplakia, syphilitic lesions and others It must be noted however that this phenomenon occurs only rarely

This controversy regarding the malignant versus the granulomatous etiology of lymphoma like cutaneous diseases is reflected in the articles of Liechti (211) and Eichler and Rottmann (97) On the basis of the histology of early and small lesions Liechti was convinced that the process was granulomatous at first and that large-celled infiltrations with many mitoses destructive growth infiltration and perforation of the blood vessel walls were merely expressions of a late facultative assumption of malignant characteristics The malignant etiology expressed chiefly by Ewing (100) and Fraser (114b) in the United States is denied by Eichler and Rottmann (97) They maintained that there is no evidence that the original cutaneous infiltrations or the alleged metastatic visceral tumors are reticulum cell sarcoma They are of the opinion that the entire process is that of a specific infectious granuloma

E Summary

Mycosis fungoides a disease of the reticuloendothelial system is described as occurring in one of three forms the classical (Alibert) type the d emblee form and the "erythroderma" form It is my opinion that only the classical (Alibert) type should be considered mycosis fungoides since this condition follows a distinctive natural clinical course beginning with chronic eczema or an eczematoid dermatitis (premycotic stage) followed by the infiltrative stage and finally progressing to cutaneous tumors The duration of the disease from the premycotic to the tumor stage may be very long This long duration is not characteristic of any other so called "lymphoblastomatous disease In view of the typical clinical course and the characteristic histologic picture it is suggested that classical mycosis fungoides should be classified as a disease *sui generis* and not be included in the lymphoblastoma dumping ground

The condition described as the d emblee" form is not mycosis fungoides This type is usually lymphosarcoma or occasionally the primary manifestation of Hodgkin s disease for it has the specific histologic picture of either lymphosarcoma or Hodgkin s disease

The condition described as the erythroderma" form is never mycosis fungoides but is a manifestation of chronic lymphocytic leukemia Hodgkin s disease or lymphosarcoma

Even though there may be a possible relationship between certain conditions in this group and even though an etiological relationship may eventually be proved it appears to be incorrect and misleading at the present time to classify this entire group of diseases as lymphoblastomas inasmuch as each presents a distinctive clinical and histologic picture

Through usage the term mycosis fungoides has become a significant clinical entity to the dermatologist and for this reason should be retained with reference however only to classical mycosis fungoides

Until we have a better understanding of the etiology of the various lymphomas it appears best to classify these diseases

as separate but related entities Any rational system of classification must depend upon the discovery of the etiological factors Until that time, classical mycosis fungoides (Alibert) should be considered as a disease *sui generis*

VI

PATHOLOGY

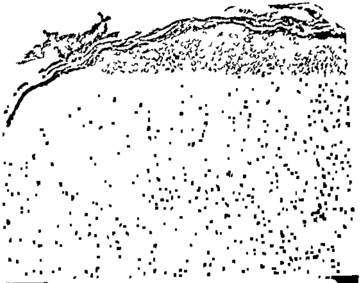
THE PATHOLOGY of mycosis fungoides has been described in detail by Poulsen (278), Galloway and MacLeod (120), Knowles (186), Montgomery (245c), Gans (121), Kyrle (193) and Winer (365)

The pathological picture can be described in two definite histologic divisions, one, the premycotic stage, the other the tumor stage

A. Premycotic Stage

Epidermis. The epidermal changes are secondary and consist of acanthosis (thickening of the prickle cell layer) and micro abscesses of Pautrier which are filled with lymphocytes and monocytic cells These cellular nests are seen around the pilosebaceous openings, on the sides of the glands, and may leak out into the gland cavity There is also liquefaction necrosis of the basal cells and, in cases where scaliness is a marked feature, nuclei persist in the most superficial layers of the stratum corneum The presence of inter-epithelial edema gives rise to the formation of reticular spaces and results in elongation of the rete pegs

Cutis The initial changes occur in the corium Apparently the process begins with dilatation of the subpapillary blood vessels and cellular infiltration surrounding these vessels The characteristic cellular infiltration is seen first in the subpapillary layer of the cutis, then extends into the papillae and laterally into the upper corium At first the cellular infiltration is outside the blood vessels, surrounding the hair follicles sebaceous glands, hair muscles and coil gland ducts while here and there, independent of these structures, the infiltration





14 Epidermal changes showing spongiosis and acanthosis
15 Pautrier's abscesses showing collections of lymphocytes and monocytes in the epidermis

VI

PATHOLOGY

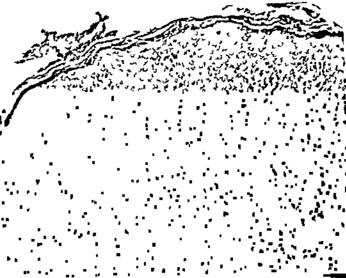
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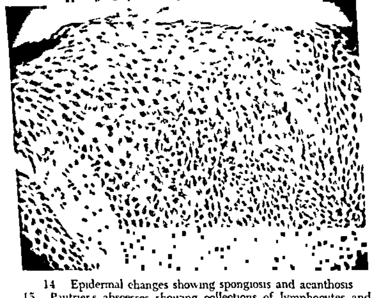
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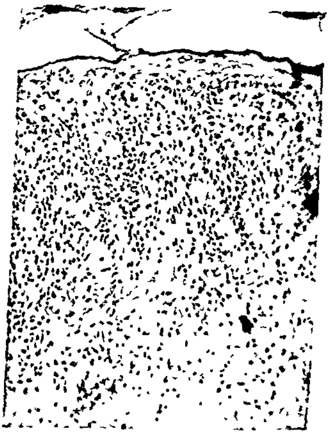
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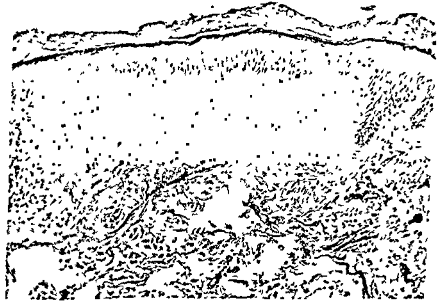
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18 Dilatation of subpapillary blood vessels and beginning cellular infiltration around these vessels

19 Characteristic infiltration in the subpapillary layer of the cutis





16 Liquefaction necrosis of the basal layer

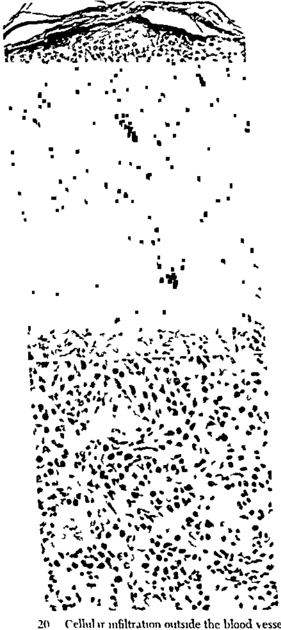


20 Cellular infiltration outside the blood vessels
21 Cell in serum (Bluefarb and Steinberg Ann Int Med Feb 1952)

spreads along the lymphatic spaces between the connective tissue bundles Although the infiltration is first found around the blood vessels, it does not necessarily arise from them The blood vessels in the papillae and in all portions of the corium become dilated, filled with blood, and give the tumors a tense, cushion-like consistency The infiltration gradually becomes more diffuse and massive and may invade the vessel walls and enter the lumen, resulting in both dilated and obliterated vessels

The infiltrating cells and the extraordinary diversity of the cells of the infiltrate, namely, polymorphonuclear neutrophils, eosinophils, plasma cells, connective tissue cells, phagocytic histiocytes, nests of reticuloendothelial cells, and pyknotic and fragmenting nuclei, are the most striking histologic features This enormous degree of polymorphism of the cells was aptly described as a "cell museum by Unna (344) Zoon (376) stated that the polymorphous picture is so typical that it is impossible not to recognize this disease Hematologists would classify this stage of mycosis fungoides as a complex reticulum cell proliferation because of its polycellular nature The nuclear changes result from intense liquefaction necrosis, which causes the cytoplasm of the proliferating cutis cells to have a "washed out" appearance, and is characteristic of mycosis fungoides In this phase Gans (121), Ormsby and Montgomery (261d) and McCafferty and Machacek (222) stressed the pyknotic nuclei, karyorrhexis and phagocytosis of pigmented granular elements of debris There is also a tendency to clumping of the reticulum cells to form pseudogiant cells which are readily differentiated from Sternberg-Reed cells of Hodgkin's disease by the nuclei and nucleoli

Jaffé (168) emphasized the increase of eosinophilic leukocytes in this stage, but Poulsen (278) did not consider eosinophilia to be of importance since it was infrequent in her series of cases Nevertheless, eosinophilia is an important diagnostic point and may be present in any stage, although it is more frequent in the tumor stage The more malignant the mycosis fungoides, the fewer the number of eosinophils



20 Cellular infiltration outside the blood vessels

21 Cell in istum (Bluefarb and Steinberg *Ann Int Med* Feb 1952)

Unna (344) was one of several observers to note that the infiltration was confined to the upper one third of the corium However, the infiltration may extend to the epidermis and may even enter the epidermis (See Illustrations 26 & 27) Although in the early lesions the infiltrate is confined to the upper one-third of the corium, it may, as the disease advances, spread to the deepest parts of the corium, around the coil glands, and may even invade the subcutaneous areolar tissue As the premycotic stage progresses, the cellular deposit becomes more abundant, according to Knowles (186) The cells show a distinct tendency to a massing, linear arrangement, both parallel to the skin surface in the subpapillary layer and with the rete pegs The cellular infiltration tends to fill all the *subpapillary portion of the corium and the papillae are filled* with new cells Meanwhile, the interpapillary spaces have become narrowed by broadening of the rete pegs, which tend, particularly in the lower portion, to be invaded by cellular masses, as the tumor stage is reached The connective tissue and elastic fibers are less evident, and the connective tissue appears wasted, resulting in closely packed cells present in the meshes of fine reticulum

B. Tumor Stage

Epidermis. The cellular outlines are frequently obscured by edema of the basal cell layer and cannot be clearly distinguished The elongated and broadened rete pegs now tend to run together,* and form a more or less continuous thickened layer with practically no papillary invaginations excepting where, here and there, a thin prickle cell layer projection is present below the confluent basal cell layer As the tumor stage advances the widened and continued rete pegs become thinner from pressure of the cell masses, which solidly fill the subpapillary portion of the corium All layers of the epidermis, particularly the rete which was previously markedly hypertrophied, become compressed and thinner as pressure of the

* *See Illustration 23*



22 Papillae filled with new cells
23 Broadening of the rete pegs

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infiltrate increases and the epidermal covering is eventually destroyed with resulting ulcerative tumors Rarely, the entire epidermis is invaded obscuring the outlines of the epidermis

Cutis The predominant cell in this stage is the characteristic reticulum cell or "mycotic" cell which is large oval and has a granular basophilic cytoplasm usually with a single nucleus which stains less deeply than other parts of the cell The nucleus is evident by its more deeply stained nuclear membrane and by showing one or more nucleoli Paltauf (265c) believed these cells to be characteristic of mycosis fungoides Fraser (114a) was of the opinion that the essential mycotic cell is of mesenchymal origin and Klemperer (185) described it as an embryonal cell According to Weidman (352a) the histologic findings indicate that these cells are derived from the endothelium of the small blood vessels Swelling of the cells within the vessel so alter them that after migration into tissues they can no longer be called endothelial cells Lapiere (197b) and Margarot *et al* (233) stated that these cells originate from histiocytes of perivascular tissue The cytoplasm in these cells enlarges and becomes more granular while the chromatin in the nucleus becomes irregular Thus one can reconcile the frequent observation of phagocytic cells together with the plasma cells which are considered more mature forms of the histiocytes The presence of reticulum mitotic figures indicates another of the multiphasic possibilities of reticulum proliferation This characteristic finding has caused confusion and resulted in a gross grouping of "lymphoblastoma" rather than a classification of the several types of reticulum proliferation Jaffe (168) believed these cells usually originate from the local histiocyte and occasionally from the fibrocyte and are present in all stages but most marked in the tumor stage

Thus mycosis fungoides is described as a reticuloendotheliosis of the skin by Berger and Vallee (26) Winer (365) concluded that the malignant reticulum cell is synonymous with the mycotic cell found histologically This same cell was called an "undifferentiated blast cell" by Downey (88) who

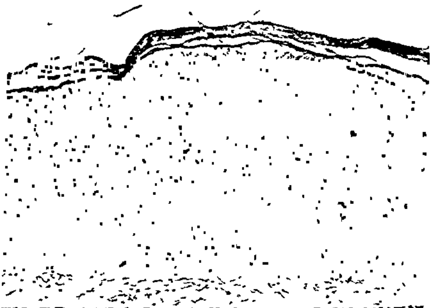


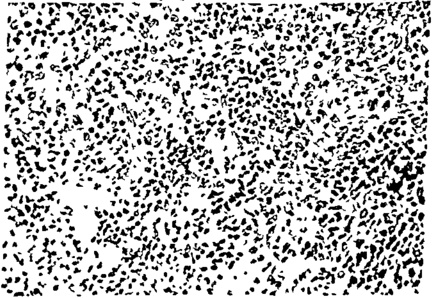
24 Closely packed cells present in the vessels of fine reticulum

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26 Invasion of the epidermis by the cellular infiltrate
27 Close up of illustration 26

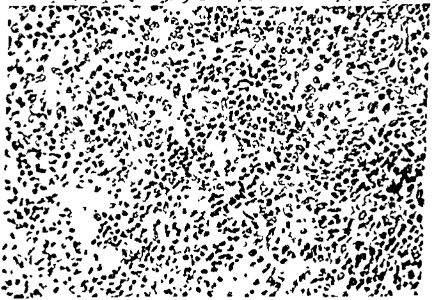
studied cellular imprints from a typical mycosis fungoides tumor

In addition to mycotic cells there are usually innumerable eosinophils distributed irregularly throughout the infiltrate and in the lumen of the capillaries Although eosinophils are not always present as mentioned previously a great number of these cells are fairly diagnostic of mycosis fungoides and they occur in relation to the blood eosinophilia Small lymphocytes are not abundant

According to Poulsen (278) this whole picture gallery of cells lies within a network the nature of which had been a subject of much discussion although the French interpretation appears to be the most comprehensible In early fetal life various elements of the blood are formed by unspecified mesenchymal cells scattered about in the organism while later this activity is assigned to the specific blood producing organs According to this theory a remnant of these mesenchymal cells forms the perithelium of the blood vessels which constitutes part of the reticuloendothelial system From these cells all the various blood cells as well as the fixed connective tissue cells originate In response to some unknown noxious agent they would become cells encountered in the polymorphous picture characteristic of mycosis fungoides This would explain the predominance of one type of cell in some cases while different cell types are present in the other cases These cells attain their highest degree of development in the so-called "mycotic cells According to this theory there is no invasion of cells from the blood vessels but rather a local transformation of one cell form into another This view is in conflict with the prevailing conception of origin development and mutual relation of the blood cells in keeping with which we must assume that the infiltrations consist of cells originating from the blood with the exception of proliferating local reticulum elements

The active hyperplasia of connective tissue cells evident at first in the corium is fairly characteristic of the disease Subsequently these cells break down and form the disintegrated mass previously described and there is a tendency for the hair





26 Invasion of the epidermis by the cellular infiltrate
27 Close up of illustration 26

cells connective tissue cells plasma cells few lymphocytes varying numbers of polymorphonuclear leukocytes and typical mycotic cells

2) The superficial location of the infiltrate in the cutis particularly in the early stages

3) The fine or coarse deeply staining granules which are remains of degenerated nuclei and the eosinophilic granules which are remains of protoplasm of degenerated cells

4) Inclusion of infiltration cells (lymphoblasts or monocytes) within the epidermis the so called Pautrier s abscesses"

5) The increase of lattice fibers (gitterfasern) in all three stages

C Histologic Differential Diagnosis

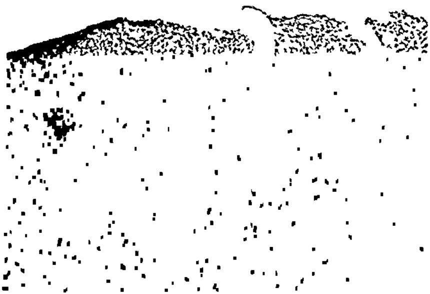
Histologically mycosis fungoides must be differentiated from all granulomas particularly tuberculosis syphilis reticulum cell lymphosarcoma leukemia and Hodgkin s disease of the skin

Syphilitic granuloma is characterized by an increase in plasma cells and the greatest cellular infiltration is present around dilated blood vessels while cell proliferation is less polymorphous than in mycosis fungoides The characteristic cell crenation and fragmentation present in mycosis fungoides does not occur in syphilitic granuloma

Tuberculous granuloma is composed mainly of lymphocytes epitheliod and giant cells and the cellular composition is even less polymorphous than that of syphilitic granuloma There are giant cells with central caseous degeneration which are not present in mycosis fungoides The collagenous bundles disappear early in tuberculous granuloma while fibrous tissue disintegrates and disappears at a very late stage in mycosis fungoides

Histologically reticulum cell lymphosarcoma is still confused with mycosis fungoides and many investigators including Winer (365) and Fraser (114b) believed the tumor stage of mycosis fungoides to be *similar* to reticulum cell lymphosarcoma

follicles to be destroyed Pathological changes in apparently normal skin have been described by Strobel and Hazen (326) and Leredde (207) Galloway and MacLeod (120) found neither destruction nor an increase of collagen in the early stages of the disease but found the collagen to have a basophilic reaction with a tendency to disintegration in the later stages There is a definite increase of reticulum gitterfasern



28 Increase of gitterfasern or lattice fibers

or lattice fibers in all stages of the disease as well as proliferation of the endothelial cells lining the blood vessels of the cutis These facts would appear to warrant the assumption that mycosis fungoides is a disease of the reticuloendothelial system It was the opinion of Woltram (370) that a diagnosis of mycosis fungoides can be made by the presence of a polymorphic infiltration and the presence of the lattice fibers

The pertinent histologic findings in mycosis fungoides may be listed as

1) A polymorphous variegated infiltrate in the cutis consisting of numerous eosinophils, lymphoblasts, fibroblasts, mast

VII

SYMPTOMS

Mycosis fungoides was formerly believed to occur in one of three types 1) Classical (Alibert and Bazin) 2) "Erythroderma" (Hallopeau and Besnier) and 3) Tumor d'emblée (Vidal and Brocq)

A Classical Mycosis Fungoides

The initial stages of mycosis fungoides are not indicative of the grave fatal outcome because of the insidious onset of the disease The classical form develops in three stages premycotic infiltrative and tumor formation There may be an interval of weeks or years between the development of these stages although one stage may supervene imperceptibly into the other or the different stages may overlap one another

1 Premycotic Stage (Eczematous Stage of Kaposi) The prodromal symptoms may be fever and joint pains Lapiere (197a) stressed the occurrence of fever as an early important symptom He stated that these symptoms are most frequent in young persons in whom the disease develops rapidly with septicemia and "rheumatic symptoms Wertheim and Smith (358) described a patient who developed a *remittent fever* during the last few weeks of illness which lasted for seven days with a nine day interval between The fever coincided with acute inflammation softening and disintegration of enlarged lymph nodes and it was assumed that secondary invasion of these nodes by pyogenic bacteria caused the *fever*

Pruritus which may be the initial or only *symptom* may precede the premycotic eruption by as long as ten years This pruritus usually generalized is often described as "persistent and intolerable" and is not relieved by any form of therapy

The granuloma always originates in the deeper layers of the skin in leukemia or Hodgkin's disease with cutaneous involvement. It is usually at the junction of the reticular layer and the subcutaneous tissue in the form of perivascular sheaths of lymphocytes and never reaches the epidermis, being separated from it by a narrow zone of connective tissue. The vessels of the cutis are markedly edematous in leukemia cutis, according to Nekam (250), with active diapedesis from the vessels, and the adjoining cutis is infiltrated with lymphocytes which follow the lymph spaces, radiate along the vessels and rise to the skin surface along hair follicles and sweat ducts. Nekam believed this infiltration to be purely leukocytic and the marked fixed cell proliferation, mitosis or imperfect giant cell formation found in mycosis fungoides, were not present. Leredde (207) stated that leukemia may, at times, simulate mycosis fungoides histologically, although his histologic studies revealed only lymphocytes. This was also the finding of Pardee and Zeit (266) who described their case as one of mycosis fungoides. The noteworthy observation that mitosis is not present in leukemia cutis has been made by Pinkus (274), Nekam (250), Nicolau (254) and Oertel (257).

The plasma cells, frequently found in the early stages, and less frequently in the tumor stage of mycosis fungoides, are not present in leukemia, according to Paltauf (265c). In a case of granulocytic leukemia, reported by Rolleston and Fox (294), the cellular infiltration involving the middle and lower corium rather than the upper corium consisted of lymphocytes and polymorphonuclear leukocytes located primarily around blood vessels from which they appeared to be exuded rather than produced in situ.

The nuclear and protoplasmic detritus present in mycosis fungoides is never found in Hodgkin's disease. Although the typical Sternberg Reed cells may be difficult to find in a single histologic section, the cells can be found in serial sections in all cases of true Hodgkin's disease of the skin.

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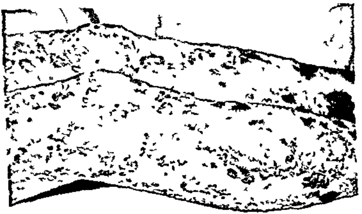
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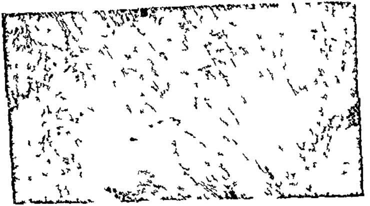
29 Eczematoid premycotic lesions (Bluefarb and Schwartz *Arch Dermat* Feb 1956)



30 Psoriasiform premycotic lesions

Its severity is frequently out of all proportion to any visible cutaneous changes and is regarded as a valuable diagnostic aid in early stages of the disease However, its presence is not constant Pruritus is usually the predominant symptom during the entire course of the disease but there are occasional reports of patients who did not have pruritus Stokes (322) described such a case and stated that the premycotic stage could continue for years without appreciable pruritus since this is a "highly individual symptom depending on the threshold of irritability of the patient's nervous system quite as much as on his skin" Fraser's (114a) patient presented the unusual clinical features of pruritus for three years, without demonstrable cutaneous changes This mode of onset is mentioned by Sequeira (311b) whose patient developed tumors immediately after a long period of pruritus, thus omitting the so called premycotic stage

The cutaneous eruption in this stage is described as polymorphic with an incredible multiplicity of phenomena Although syphilis has been termed the great imitator in dermatology, this description applies equally well to mycosis fungoides Many dermatologic possibilities often occur in a single case ephemeral erythemas urticaria, hemorrhage (O'Leary *et al* 258h Gordon 137, Goeckerman and Montgomery 132), bullae, psoriasiform, erysipeloid, trichophyton like and eczematous types of eruptions The cutaneous surface may show only fine scaling, there may be areas of thickened exfoliation or crusted aggregations having pinpoint oozing All transitions between simple transitory erythema with localized flat or macular lesions of various sizes are possible The first manifestations of the disease are transitory, with complete evanescence, usually leaving no evidence of having been present Parapsoriasis-like types usually present a more solid appearance and develop as superficial flat papules In the early stages, the lesions tend to crop out from a single focus of the disease, advancing peripherally with central healing They begin with curved and circular efflorescences simulating the intact erythematous scaling the oozing aspect of the disease,



33 Erythematous premycotic lesions

that of these benign conditions The multiple sharp margins more prominent in the foreground are yellowish red in color and occasionally pigmentation is a striking characteristic of the early stage

Case Report A 69 year old woman first developed a dry scaly cutaneo s eruption wh ch d d not improve with treat ment F ve years later a 4 cm cutaneous lesion appeared on the right s de of the back which was removed s rgically healed well an l roentgenotherapy was g ven to th s area Ho vever a pa nless elevated lesion soon appeared in the left supra clav cular reg on and became ulcerated On examination there was a general zed dry patchy scaling slightly pruritic cutaneo is eruption Some of the les ons were slightly erythe mato s and some were sl ghtly ra sed infiltrated plaques A crusted les on was present in the left supraclavicular region Small lymph nodes vere present in the ax llae and larger lymph nodes in both inguinal regions The l ver was palpable

The fact that these early eruptions do not exactly correspond to any common cutaneous disease is a valuable diagnostic aid The numerous descriptions of these eruptions usually include *intermediate* " "eczematoid " "lichenoid " "psoriasiform" and eryth rodermal " Lesions described as raised pad like in

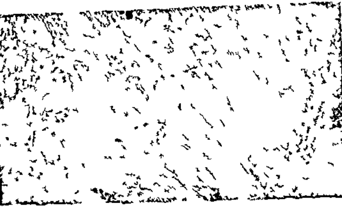


31 Trichophyton like premycotic lesions



32 Ulcerated bullous premycotic lesions

or as a fleeting erythema which simulates a superficial trichophytosis The appearance of thickened scales the spontaneous course and healing without scar formation simulates psoriasis and makes the differential diagnosis from superficial scaling dermatoses difficult However the color differs from



33 Erythematous premycotic lesions

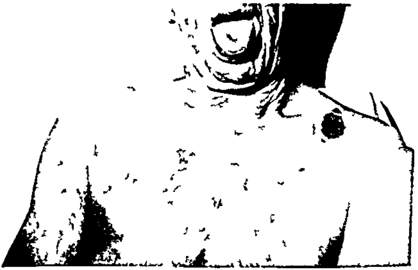
that of these benign conditions The multiple sharp margins more prominent in the foreground are yellowish red in color and occasionally pigmentation is a striking characteristic of the early stage

Case Report A 69 year old woman first developed a dry *scaly cutaneous eruption which did not improve with treatment* Five years later a 4 cm cutaneous lesion appeared on the right side of the back which was removed surgically healed well and roentgenotherapy was given to this area However a painless elevated lesion soon appeared in the left supraclavicular region and became ulcerated On examination there was a generalized dry patchy scaling slightly pruritic cutaneous eruption Some of the lesions were slightly erythematous and some were slightly raised infiltrated plaques A *crusted lesion* was present in the left supraclavicular region Small lymph nodes were present in the axillae and larger lymph nodes in both inguinal regions The liver was palpable

The fact that these early eruptions do not exactly correspond to any common cutaneous disease is a valuable diagnostic aid The numerous descriptions of these eruptions usually include "intermediate" "eczematoid" "lichenoid" "psoriasiform and "erythrodermal" Lesions described as raised pad like in



34 Scaly and crusted papular lesions of the premycotic stage (case report)
35 Scaly and crusted papular lesions of the premycotic stage (case report)



36 Ulcerated tumor in the left clavicular region (case report)

filtrated erythematous persistent patches usually cresentic or discoid but occasionally completely circular are frequently pathognomonic They appear as small red papules in the





37 Circular disc or ring formation
38 Circular disc or ring formation

formation of rings or circular discs tending to form round or *oval sheets* with well defined borders The lesions vary from 2 cms to 15 or more cms and may coalesce and form gyrate figures with areas of normal skin between the lesions, producing a very striking cutaneous picture



39 Coalescing of rings forming gyrate figures

The papules *sometimes resemble* urticaria *psoriasis, eczema* or psoriasiform parakeratosis, and are at first transitory but later become persistent The most common premycotic eruption is the eczematous type which usually appears as a small round plaque resembling circumscribed psoriasiform parakeratosis (Lapiere 197a) which develops into a plaque of localized neurodermatitis The plaque may be present for

several years may disappear with local therapy or may recur at another site. The long duration of intense pruritus and progressive infiltration all tend to arouse suspicion concerning the lesions which vary from yellow and red to reddish violet in color with a slightly scaling surface. Lichenification and eczematization due to the intense pruritus may be secondary manifestations. This initial lesion was called the primary lesion or "chancre of innoculation" by Hallopeau and Bureau (145d). This lesion shows a predilection for the back of the trunk



40 Psoriasiform type of mycosis fungoides

especially the scapular regions although other areas of involvement have been reported. Lesions on the legs, arms and buttock were described by Sequeira (311b), the *forearm* by Stowers (324a, b), the leg by Breakey (47), the thigh by Towle (337), Post and Lincoln (277) and O'Leary *et al* (258f), left flank by Oliver and Bluefarb (259f), left hip by Orbel (260), the external malleolus by Ullmann (343), the abdominal wall by Crocker (71b), the eyelid by Dubreuilh (90), the scalp by Lavmon (202) and the back by O'Leary *et al* (258h) in a woman who was two and one half months pregnant.

Other types of lesions which may be present during the

formation of rings or circular discs tending to form round or oval sheets with well defined borders The lesions vary from 2 cms to 15 or more cms and may coalesce and form gyrate figures with areas of normal skin between the lesions producing a very striking cutaneous picture



39 Coalescing of rings forming gyrate figures

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42 Mycosis fungoides of the left flank

premycotic stage are red or purplish macules and urticaria Patches of irregular outline suggesting seborrheic dermatitis were mentioned by Wise (368h) others suggesting psoriasis were reported by Miescher (239) and Bernstein and Goldberger (30) These patches may present a lichenoid oozing or crusted surface but are rarely pustular and may involve any portion of the body as well as the face neck and extremities The palms and soles are usually spared and the lesions tend to be more marked over the lower half of the body The lesions become thick and infiltrated forming round hard patches of varying shades of red disappear and recur in the same areas leaving pigmentary changes which are more or less permanent The concave border of these lesions is a characteristic finding with apparently normal skin penetrating convexly into the premycotic areas They are often circinate or gyrate and may result in central atrophic depressions The surface is prominent smooth and shining as a result of orbicular patches with marked edematous infiltrations of the corium A zoniform distribution as reported by Blum and

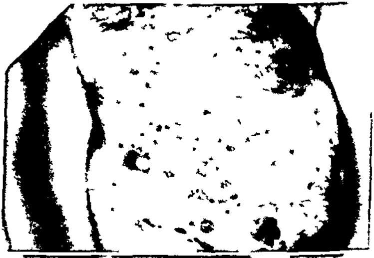


41 Plaque resembling localized neurodermatitis



45 Lesion on buttock showing concave border

Lanos (39), is rare.* The constant scratching and rubbing modify the eczematous lesions although there are no scratch marks in spite of the intense pruritus. The scaly surface and eczematous lesions simulating weeping eczema are present in





43. Lesions of mycosis fungoides leaving pigmentation
44. Lesions of mycosis fungoides leaving pigmentation

islets surrounded by normal appearing skin. C. G. Lane (195a) was of the opinion that spontaneous involution occasionally occurs and he described patients who had become resistant to

* See Illustration 42



45 Lesion on buttock showing concave border

roentgenotherapy Although therapy was discontinued lesions continued to appear and disappear without further treatment He described another patient whose lesions progressed slowly in a band-like formation, of finger-breadth width, across the side of the chest, leaving apparently normal skin, until the borders of the lesions finally merged A patient who had numerous cutaneous lesions resembling a fixed eruption was reported by Chargin (60)

Flat bullae, which become impetiginous from infection, or spontaneous bullae, in cases having rapid evolution, may appear secondarily Generalized bullous lesions, simulating pemphigus, which appeared in the terminal stages of the disease, were described by Goeckerman and Montgomery (132) The bullous lesions of mycosis fungoides must be differentiated from those attributed to iodides, as in the fatal case reported by Eller and Fox (98i), as well as from bullous lesions which probably result from multiple, malignant epithelial proliferations of epidermal structures, as described by Goeckerman and Montgomery (132), Ketron and Goodman (181) and Montgomery (245c)

Patients having bullae resembling pemphigus were reported by Curtis *et al* (73b), Hallopeau and Railliet (145k), Kaposi (176b), Reines (290), and Wills (363a) A 30 year old woman, described by Lortat-Jacob and Le Grain (217), had polycyclic, non pruriginous, painful cutaneous lesions which were followed by bullous ulcers Bullous lesions were also noted by Musso (249) A 19 year old woman who developed bullous lesions over large lichenified areas was reported by Sequeira (311b) The lesions, which appeared on the thigh rapidly spread to the buttocks, thighs, arms, and back, and became pigmented Post and Lincoln (277) reported a patient having bullous cutaneous lesions on the palms and soles

Occasionally bullous lesions which occur in crops in the interval of the premycotic eruption resemble dermatitis herpetiformis Sequeira's (311b) patient a 64 year old man, had urticarial and papulovesicular lesions on the trunk and extremities which resembled dermatitis herpetiformis Wills

and Hadfield's (363c) patient a 31 year old man had urticarial, vesicular pigmented cutaneous lesions which resembled dermatitis herpetiformis Premycotic lesions resembling dermatitis herpetiformis were also described by Pernet (271b) and Pringle (280c case 4)

A 54 year old woman reported by O Leary *et al* (258f) developed pruritus and erythema of the arms and neck five years previously which was followed by a bullous eruption on the ankles Thickening and exudation of the skin of the legs thighs and abdomen appeared ten months previously Although the pruritus had decreased the skin had not been entirely clear since the onset Hemogram revealed eosinophilia and monocytosis the sedimentation rate was 50 mms in one hour (Westergren) Histologic examination of a cutaneous lesion from the back showed mycosis fungoides while a cutaneous abdominal lesion revealed eczematoid dermatitis

A patient having bullous lesions which were mistaken for pemphigus by several competent dermatologists was described by Garb and Wise (122f) The bullous lesions appeared in infiltrated nodules and plaques as well as on clinically normal skin They believed bullous and vesicular lesions to be extremely rare in mycosis fungoides but occasionally occurred because of interference with circulation of lymph thus causing secondary "wet" lesions as opposed to the "dry" primary lesions For example Wise and Eller (368k) described bullous lesions occurring in association with Kaposi's sarcoma which is ordinarily a "dry" eruption These secondary elements are caused by blockage of the flow of lymph

A 67 year old man with bullous lesions on the palms and soles was described by Wise (368h) The lesions were multiform and symmetrical consisting of thin walled vesicles and bullae some distended some flaccid and ruptured and plaques and superficial discoid patches The areas not involved in this process appeared normal There was marked involvement of the flexural surfaces and the entire scalp was studded with "pea to almond" size hemorrhagic raw crusted areas The vesicles and bullae had first appeared on the scalp face neck and

upper back but had spread to involve the trunk and limbs during the preceding two months The bullae usually developed in the center of plaques and superficial patches, and varied from "pea to cherry" size, although some were the size of a "small egg" and contained clear fluid They were fairly firm at the onset but later collapsed and ruptured, leaving raw, denuded areas, some hemorrhagic

In describing the premycotic stage, Ormsby and Montgomery (261d) stated in their textbook that vesicles or bullae are occasionally present and they had observed annular lesions some vesicular or bullous, in patients having mycosis fungoides A woman with generalized mycosis fungoides who had a few small bullae on the abdomen was presented by O'Leary *et al* (258h) Belot (23) cited the case of a 69 year old man who had one bulla on the wrist and who had at one time bullae on the corneas Wile and Knerler (362d) reported the occurrence of mycosis fungoides in mother and daughter The daughter had vesiculation of the palms and soles at the onset and later the eruption became widespread to involve the face and neck Lortat Jacob and Le Grain (217) described a 36 year old man who had bullous ulcerative lesions of cyclic or polycyclic arrangement It is stated in Jadassohn's (167) posthumous work, that bullae similar to those which occur in pemphigus and dermatitis herpetiformis rarely occur in mycosis fungoides It is not stated in the aforementioned reports, except by Ormsby (261a), whether the bullae arose from the infiltrated mycosis fungoides lesions Garb and Wise (122f) believed it may be justifiably assumed that the bullae are independent lesions and do not arise from the active plaques and patches They could find no histologic descriptions or photomicrographs showing as in their case the presence of bullae arising from the lesions of mycosis fungoides The designation mycosis fungoides bullosa is suggested as being applicable to their case in preference to mycosis fungoides with bullous lesions, in analogy to lichen planus bullosus, lupus erythematosus bullosus and erythema multiforme bullosum

The patient described by Trimble (339a) had prefungoid

lesions consisting of scaling and infiltrated patches for a period of 25 years Gate *et al* (124a) reported a patient who had premycotic erythema under the lesions of crustaceous scabies A patient described by Scheer (304) had mycosis fungoides which was obscured by the clinical picture of lichenified eczema A patient reported by Levine (209) had a condition which was diagnosed as pruritus of pregnancy but postpartum she developed typical mycosis fungoides

The duration of this primary stage appears to vary considerably Although it is usually present from two to five years, it is occasionally reported to be very transient On the other hand temporary spontaneous remissions may lengthen this period considerably Both Davies (75) and O'Donovan (256b) described patients who apparently had the disease for about 30 years A 78 year old man presented by Lyons (220) had many large irregularly shaped lesions on the trunk and extremities particularly the lower extremities The lesions were slightly elevated sharply marginated and infiltrated some forming large plaques and patches A mass the size of a "hen's egg" was present on the right thigh The cutaneous eruption of a dull pink color was extremely pruritic He improved with roentgenotherapy and the diagnosis of mycosis fungoides was proved histologically This patient had been treated by Abramowitz (1a) ten years previously and by G H Fox (110) before that The duration of the disease was therefore approximately 30 years

2 *Infiltrative Stage* The first stage or *eczematous* cutaneous lesions do not always occur in mycosis fungoides The disease may begin with lesions of the infiltrative stage The variegated eruptions of the premycotic stage gradually subside while the infiltrations increase with brick red patches of cushion like consistency having a tense shiny surface and are granular or verrucous A generalized infiltrative form with lichenoid papules was described by Rattner and Rodin (287)

There is a reddish blue halo outside the peripheral infiltrated propagation" zone indicating the extent of the process The appearance and location of the elements change rapidly dur

upper back but had spread to involve the trunk and limbs during the preceding two months. The bullae usually developed in the center of plaques and superficial patches, and varied from "pea to cherry" size, although some were the size of a 'small egg' and contained clear fluid. They were fairly firm at the onset but later collapsed and ruptured, leaving raw, denuded areas, some hemorrhagic.

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There is a reddish blue halo outside the peripheral infiltrated propagation" zone indicating the extent of the *process* The appearance and location of the elements change rapidly dur

ing this stage, large, flat, smooth infiltrations may become extensive ulcerations within a few days New infiltrations appear, while the old ones disappear leaving either no trace pigmentation or, rarely, atrophy. This was demonstrated in Fraser's (114a) patient who had one lesion which was a com





46 Infiltrative stage consisting of patches of cushion-like consistency

47 Infiltrative stage consisting of patches of cushion like consistency

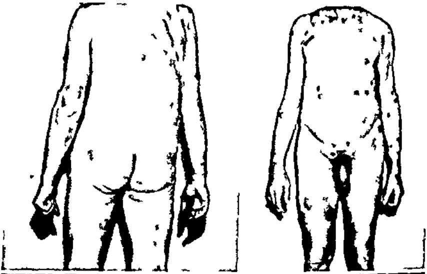
plete elevated ring This lesion disappeared in less than one week when another lesion of the same type appeared in another site The lesions often subside in the center while the margins remain and gradually unite into gyrate, serpiginous patterns as in the case reported by Oliver and Bluefarb (259f) There may be loss of hair in the infiltrated area as well as in areas not involved A diagnostic point sometimes overlooked in this stage is the variation in the amount of thickening and infiltration in different patches or different areas of the same patch This is well shown in the circinate plaques where one portion may not be raised above the cutaneous surface while another



45 I filt t ve stage cons st ng of patcl es of cush on l ke consist ency (close up)

area may be distinctly infiltrated and raised Objective signs of prur tus are u s ially not present scratch marks are seldom present *

* See Ill trat o 4)

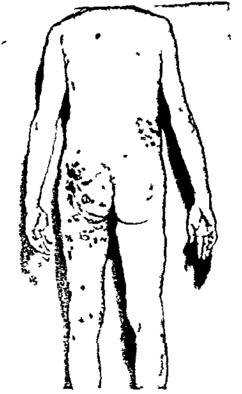




49 Infiltrative stage with beginning ulceration
50 *Infiltrative stage with beginning ulceration*

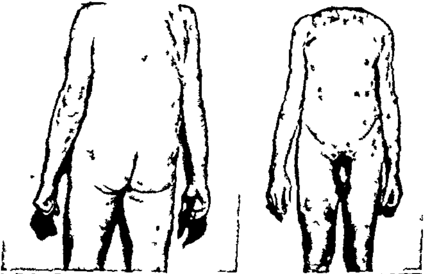
Lapiere (1973) described the elastic infiltration as having a special sensation when squeezed which an examiner who had felt the condition previously would recognize The center of the plaques *is sometimes papillomatous or verrucous*

A 63 year old woman whose only cutaneous lesions were verrucous plaques and nodules widely dispersed on the lower extremities was reported by Asel *et al* (8) She had approximately 15 well demarcated firm erythematous verrucous



51 Infiltrative stage with beginning ulceration

roughly circular plaques and nodules Milan and Perin's (241b) patient had verrucous and hyperkeratotic lesions Two similar cases were described by Jeanselme and Burnier (172) who commented on the scarcity of reports of hypertrophic and verrucous lesions in mycosis fungoides The verrucous lesions





49 *Infiltrative stage with beginning ulceration*
50 *Infiltrative stage with beginning ulceration*

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around the nipples and areola Thomson's (3321) patient was a 39 year old woman who developed an overgrowth of the left areola and nipple three years previously and similar changes occurred in the right breast nine months later This condition remained unchanged for two years A diagnosis of Paget's sarcoma was made and a mild indefinite cutaneous eruption of the arms and legs was attributed to xeroderma Histologic examination at that time was not diagnostic of mycosis



53 Vegetative and hyperkeratotic lesions

fungoides Fifteen months later a marked pruritic infiltrated eruption with islands of apparently normal skin appeared on the abdomen and a typical red scaling eruption on the scalp

The lesions in the infiltrative stage are usually persistent although some may resolve and leave patches of pigmentation. The scalp may become grossly scaly and the hair may become extremely thin While the greater portion of the body may be involved mouth lesions are rare The nails often become thick discolored and misshapen and are sometimes shed General

in all three of these cases were covered with thick, large, adherent scales and were sometimes dry and fissured and, at times, ulcerated with a serous discharge In addition to the verrucous lesions, these patients also had other manifestations of mycosis fungoides Reich and Bonse (289a) also emphasized the vegetating and hyperkeratotic lesions Their patient



52 Gyrate and serpiginous lesions

was a 51 year old woman who had cutaneous lesions of ten years duration which had been diagnosed and treated as psoriasis Vegetating and hyperkeratotic lesions were present in the ankle regions and on the feet We have also observed a patient who had vegetative hyperkeratotic lesions

Morris (246) reported a 28 year old woman who had unusual cutaneous manifestations of this stage of mycosis fungoides There was intense pigmentation and marked infiltration

was reported by Abramowitz (1c) He also had priapism but no nervous system involvement was apparent

According to Wise (368f) scleroderma dermatomyositis and "lymphomatoid disease are sometimes present in the same patient and he believed that Howard Fox's (112b) patient would present all these features if he lived long enough

3 *Tumor Stage* This stage develops gradually through

to Lapiere (197a) Should the lesion appear suddenly on normal skin this would be the true "d emblee type

On palpation of an infiltrated lesion which will develop into a tumor the sensation is that of a subcutaneous nodule These nodules are characteristic of mycosis fungoides according to Wickham (361)

Nodular tumors often merge into larger lobulated deeply furrowed tumors which are of a dull red color soft hemispherical and have a nodular surface These nodules have a broad base and may become fungating from constriction of the base The face back and proximal parts of the extremities are common sites of localization while involvement of the scalp is rare The intact tumors are not painful but the ulcerated ones are usually extremely painful

Sequeira (311b) stated that he had never observed mycosis fungoides in a Polish patient However we have observed such a case

Case Report A 41 year old Polish man first developed red spots 2 cms in size on the distal portions of the lower arms two years previously These lesions tended to fade during

... appeared on the back arms and legs There was no involvement of the areas distal to the wrists and ankles or of the face The size of the lesions increased and occasionally discharged a serous fluid Painless nonpruritic

ized lymphadenopathy may occur during this stage and frequently excoriation blood crusts, slight lichenification and pyogenic infection occur.

A 56 year old man, reported by Gougerot and Burnier (139c), developed intense diffuse uniform pigmentation following the erythema of a premycotic lesion. The lesions, which first appeared on the hands and feet, spread to involve the extremities and abdomen and were extremely pruritic, erythematosquamous, and infiltrated. There was a diffuse uniform brownish pigmentation and a generalized lymphadenopathy.

The majority of patients having herpes zoster associated with mycosis fungoides have the so called "d'emblee" form of the disease. Cases of this type were described by Bluefarb and Morris (38c), Semon (309) and Poulsen (278). Newman (252) reported a 59 year old women who had a generalized eczematoid dermatitis and plaques, which were histologically mycosis fungoides. The eruption cleared following nitrogen mustard therapy but herpes zoster appeared on the right scapula and breast. Roentgenogram of the spine revealed compression of the fourth dorsal vertebra. Morrow (247) reported a 54 year old man who developed an extensive zoster pectoralis on the left side following arsenotherapy (Fowler's solution). There was intense burning pain preceding and accompanying the zoster, and neuralgic pain persisted long after complete involution and cicatrization of the vesicular lesions. The redness and scaliness of the mycotic patches, on which the zoster developed, was not affected by the process. Hard, nodular elevations appeared along the lines of zoster distribution several months later.

Atrophy may occasionally follow the cutaneous lesions and usually occurs on the lower extremities as described by Ormsby and Montgomery (261d) and Kindler (183). However, Wise (368a) stated "In mycosis fungoides true atrophy of the skin with cigarette paper wrinkling is not known to occur, even in the end stages of the malady."

A 58 year old man who had mycosis fungoides for 14 years

was reported by Abramowitz (1c). He also had priapism but no nervous system involvement was apparent.

According to Wise (368f) scleroderma, dermatomyositis and "lymphomatoid" disease are sometimes present in the same patient and he believed that Howard Fox's (112b) patient would present all these features if he lived long enough.

3. *Tumor Stage.* This stage develops gradually through the appearance of tumors only in infiltrated lesions. The tumor usually appears first at the border of an old plaque of infiltration and rarely occurs in a recent area of infiltration according to Lapière (197a). Should the lesion appear suddenly on normal skin this would be the true d'emblée type.

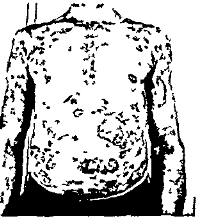
On palpation of an infiltrated lesion which will develop into a tumor the sensation is that of a subcutaneous nodule. These nodules are characteristic of mycosis fungoides according to Wickham (361).

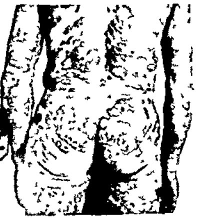
Nodular tumors often merge into larger lobulated, deeply furrowed tumors which are of a dull red color, soft, hemispherical and have a nodular surface. These nodules have a broad base and may become fungating from constriction of the base. The face, back and proximal parts of the extremities are common sites of localization while involvement of the scalp is rare. The intact tumors are not painful but the ulcerated ones are usually extremely painful.

Sequeira (311b) stated that he had never observed mycosis fungoides in a Polish patient. However, we have observed such a case.

Case Report. A 41 year old Polish man first developed "red spots" 2 cms in size on the distal portions of the lower arms two years previously. These lesions tended to fade during warm weather and became more pronounced in cold weather. They were intensely pruritic and were aggravated by sweating. One year after the appearance of these lesions they began to increase in number and appeared on the back, arms and legs. There was no involvement of the areas distal to the wrists and ankles or of the face. The size of the lesions increased and occasionally discharged a serous fluid. Painless nonpruritic

ulcerating tumors then appeared in the axillae, on the arms and at the waist. Although the tumors healed spontaneously, leaving white scars two or three similar lesions would appear in the same area. He had bilateral axillary and inguinal lymphadenopathy. On examination there were dry, scaling areas of lichenification with nodular infiltration and 0.2 to 4.0 cm tumors, many of which were ulcerated, on the chest, back, abdomen, buttocks and extremities but the exposed areas of the hands and face were not involved.





54. Mycosis fungoides with beginning tumor formation (case report)

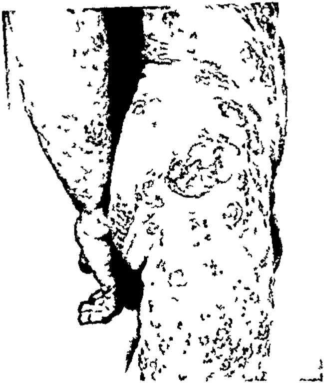
55. Mycosis fungoides with beginning tumor formation (case report) (Bluefarb and Schwartz. *Arch. Dermat.*, Feb. 1956)

The tumors are discrete and localized at the onset but increase rapidly in size and number, each tumor being *round or oval* in shape. The center is sometimes depressed, suggesting lobulation and, more rarely, it becomes pedunculated. When confluence takes place, the appearance is described as "more hideous than that of any other vegetating growth of the skin."*

The tumors are soft and semi-fluid in consistency with a "vinous" coloration and interstitial hemorrhage may result in a dark color suggesting melanotic carcinoma. The tumors may retrogress and disappear in any stage of development. Usually

* See Illustrations 10 and 11

no evidence of their presence remains and scar tissue occurs only when the tumors ulcerate They may however leave brownish pigmented macules and there is alopecia of hairy surfaces

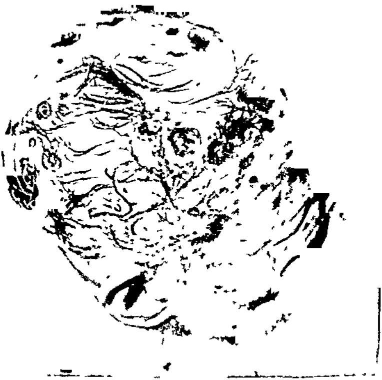


56 Mycosis fungoides with beginning tumor formation (case report)

In the last stage the tumors may disintegrate diminish in size and disappear with a pigmented atrophic scar remaining The tumors may also clear in the center and progress peripherally forming rings and circles The majority however become excavated and secondarily infected These may be large

round ulcers with a sloughing base which are invaded by pyogenic organisms and cause severe toxemia which results in the exhaustion preceding death

Trauma and friction are common causes of ulceration and result in superficial erosions The nodules often soften in the center, fluctuate and finally ulcerate leaving crater-shaped



57 Ulcers with sloughing base in a terminal stage

ulcers with ragged margins covered with shreds of tissue The ulcers usually extend only to the subcutaneous tissue, rarely to the bone The general health of the patient declines during this period and there is usually diarrhea, cachexia and fever

The tumors are described by Poulsen (278) as being from "cherry to half orange in size and the color from dark red to black, with a lobulated, tomato like appearance of semicircu

lar or polycyclic shape. As many as 3 000 tumors were present in one patient. In the ulcerative stage lymphadenopathy results from secondary infection. The temperature is usually normal or subfebrile but is rarely septic. The skin around the tumors may be normal, but if extension occurs a crop of dark red, smooth, warty, circumscribed lesions appear according to Hallopeau and Jeanselme (145g).

Soft elastic tumors which disappear under pressure were described by Kaposi (176c case 1) and Kobner (187b case 1). Auspitz (11) reported a patient with early nodules which were of bright red color and of a gelatine like transparency. Some cases present large areas of diffuse cutaneous infiltration which are thickened and of board like hardness with no pliability. The surface is dark or violet red, uneven and nodulated. Such involvement of the abdomen was described by Kaposi (176c case 5) and Kobner (187b case 2), while Gillot (128) reported this involvement of the left breast.

Although the premycotic lesions are highly pruritic, the tumors are not pruritic. Rothman (298) observed that *pruritus* was present as long as there was a defense reaction of the skin against the deposition of foreign cells. The pruritus subsided after the infiltrating tumor had become established and started unlimited growth.

A 59 year old woman reported by Campbell (57) had an area of red irregular hypertrophic granulation extending from the glabella to the upper lip and from the center of each cheek across the face. The normal configuration of the face was completely obscured, the right naris was entirely occluded and the left one partially occluded by the process. Milbradt (240) described a 46 year old woman who had tumors on a generalized atrophic skin.

The final stage of the disease is the *ulceration of the tumors* and indicates that death is imminent. The skin over the tumors becomes tender and the center becomes *ulcerated*. At first the base consists of clear bright red granulation tissue, but it soon develops into a purulent cavity as a result of secondary infection. The ulcer usually extends only to the subcutaneous

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58 Ulceration of a nodule

and eyelash hair was entirely absent and there was alopecia of the scalp which was involved by many nodular lesions covered with crusts and scales There was a fetid purulent discharge of the face and scalp lesions especially upon pressure of the vegetating lesions of the forehead The entire cutaneous sur face of the face including the eyelids and ears was thick and lichenified There were nodules and numerous violet red sharply demarcated dry infiltrated plaques on the trunk some the size of a "palm The skin of the genitalia and surrounding areas was red weeping and edematous There were several nodular infiltrations on the extremities and an infiltrated ulcera tive lesion on the anterior region of the left thigh Gross and histologic examination of an axillary lymph node suggested an inflammatory rather than a neoplastic process The diagnosis was dermatopathic lymphadenitis However the duration of the eruption severe pruritus eczematous recurrences and

tissue The ulcerated nodules are similar to those present in the ulcerative type of Hodgkin's disease, according to Durand *et al* (93)

Infiltration and nodules occurring on the face are characteristic This leonine appearance simulates that of nodular leprosy There are comparatively few reports of mycosis fungoides with leonine facies Standard dermatological text books give little or no description of this type of involvement According to Abramowitz and Kanee (1d), leonine facies occur in the second stage when there is infiltration of the cutaneous lesions as well as in the terminal stage of the disease

The first report of this condition was by Kobner (187a) in 1864 He described a 40 year old woman with frambesia like lesions on the face, trunk and extremities The histologic picture was mycosis fungoides A 60 year old man who had *tumors of the face, swelling of the face and eyelids* and lesions on the body, was reported by Demange (81) Histologic examination indicated mycosis fungoides or Hodgkin's disease A 37 year old man, observed by Gallard (119), had lesions on the trunk and on the face where deep folds and ridges produced a leonine appearance Ehrmann's (96) patient also had lesions on the trunk and leonine facies Facial lesions similar to those present in nodular leprosy were described by De Crop and Salle (78a) in a 50 year old man who lived in North Africa Lesions on the body were characteristic of mycosis fungoides and this diagnosis was confirmed histologically A 59 year old man reported by Berggreen (27), had histologically proved mycosis fungoides of 12 years duration Nodular infiltrations of the face appeared during the last year of life resulting in leonine facies Pautrier's (268d) patient was a 67 year old man with leontiasis of the face produced by large hard infiltrated tumors

Abramowitz and Kanee (1d) reported a 46 year old man who had numerous, "marble sized" nodular infiltrations on the forehead eyebrows eyelids and cheeks which produced a leonine facies There were filiform and papillomatous vegetations superimposed on the nodular infiltrations The eyebrow

patient described by Galloway and MacLeod (120) However, the woman reported by A Jamieson (169) did not improve following two attacks of erysipelas A 63 year old man, reported by Louste *et al* (218), had alopecia areata and a severe febrile disease, diagnosed as descending polyneuritis, which was followed by the rapid development of plaques and tumors which had histologic changes "ranging from ordinary inflammation to mycosis fungoides"

Highman (156c) observed one patient for five or six years and during the last month of life an exanthem resembling circinate toxic erythema suggesting toxemia, appeared The remains of these lesions appeared to be the starting point of new mycotic lesions, which ultimately became voluminous At autopsy, the viscera were also found to be riddled with tumors Buschke *et al* (53) described a 50 year old woman who had paralysis of the right side of the face and right arm Bouvier *et al* (42) reported a patient who had paraplegia resulting from an epidural mycosis fungoides nodule in the vertebral canal

During the tumor stage the patient becomes anemic and wasted and develops anorexia, dyspepsia, diarrhea insomnia and depression The pruritus, and intoxication from secondary infection causes general exhaustion and death, unless intercurrent disease such as pneumonia, results in earlier expiration

5 **Cutaneous Appendages** HAIR Loss of the hair may result from scratching It becomes thin and brittle, although a general alopecia seldom occurs Generalized alopecia was observed at the onset of the disease by Lapiere (197a) Ormsby and Montgomery (261d) stated that varying degrees of alopecia have been noted A 50 year old woman, reported by Wise (368f) had loss of the scalp hair six months before the cutaneous lesions on the body began to spread He believed this alopecia to be a usual occurrence A 26 year old woman, reported by Giovannini (130), had a universal alopecia areata preceding the development of *mycosis fungoides* and the 63 year old man described by Louste *et al* (218) also had alopecia areata

nodular lesions were diagnostic of classical mycosis fungoides The nodules were surmounted by papilloma like elevations The leonine facies was unusual the authors believed and resulted from the nodular infiltrations on the face which threw the skin into folds such as those present in leprosy

4 General Symptoms A daily fever of an extreme and debilitating degree may be present and simulate the Pel Ebstein type of fever curve present in Hodgkin s disease The importance of fever as a symptom of mycosis fungoides was stressed by Lapiere (197a) An intermittent fever with readings suggestive of malaria or septicemia was present in the patient reported by Post and Lincoln (277)

General symptoms which occurred in Poulsen s (278) patients were weight loss and night sweats in some cases diarrhea in two a hemorrhagic condition in one and arterial hemorrhage from an ulcerated tumor in one case

A severe toxic state was described by Winer (365 case 3) in one patient which he attributed to the tendency of mycosis fungoides to "resolve itself and melt away This phenomenon also occurs in cases which assume neoplastic characteristics with involvement of internal organs and regional lymph nodes and in those having replacement of normal structure by neoplastic processes containing numerous mitotic figures

Unusual manifestations due to internal organ involvement have been described Hemiplegia was reported by Brandweiner (44) epileptiform seizures by Pringle (280b) hemophilia by Quinquaud (284) and dullness and pleuritic friction probably caused by a pulmonary growth was mentioned by Sequeira (311b)

Disappearance of the tumors following intercurrent disease has occurred in several patients Alibert s (2b) patient had regression of the tumors following erysipelas A similar case was described by Bazin (17a) although Funk (117) was of the opinion that this patient had Kaposi s sarcoma The tumors disappeared during the course of fatal pneumonia in a patient described by Pringle (280a) Temporary improvement of the cutaneous lesions occurred during an attack of influenza in a

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the soft palate was reported by Corbett (66) who believed mucous membrane involvement to be rare in mycosis fungoides

A 56 year old woman who had involvement of the tongue was reported by Tolman (336) F P Mc Carthy (223) stated that illustrations of tongue lesions occurring in mycosis fungoides appear in dermatological and oral medicine textbooks He observed mouth lesions which were raised nodular and 0 5 by 3 0 cms in size In one patient, the dorsum of the tongue was white suggesting a secondary leukoplakic reaction A patient having mycosis fungoides of the pharynx occurring simultaneously with scleroderma was described by Cheridjian (61)

Involvement of the mucous membranes appears to be extremely rare in the reported cases of mycosis fungoides It is our impression that these cases are all instances of lymphosarcoma

7 *Laboratory Findings* a PERIPHERAL BLOOD There is no characteristic blood picture in any stage of mycosis fungoides Occasionally there may be an anemia and the red blood cell sedimentation rate is sometimes increased

In reviewing the literature Howles and Connell (158) found that peripheral blood changes may or may not occur in mycosis fungoides Although the majority of patients have no blood abnormality early in the disease some develop these changes later in the course of mycosis fungoides Poulsen (278) reported the lowest hemoglobin to be 75 per cent follo...

1) *Eosinophilia* Although blood eosinophilia is not a constant feature a finding of more than 10 per cent eosinophils is suggestive of mycosis fungoides The number of eosinophils varies greatly many reports indicate no eosinophils while a patient reported by Brunauer (51a) had 70 per cent

Among the reported cases of mycosis fungoides which men

NAILS No nail deformity results from mycosis fungoides However the nails become polished as a result of rubbing and are occasionally transversely stripped Garb (122b) was the first to note blackish pigmented horizontal patches at the junction of the nail plates with the free border of the nails However, this patient had received antimonials which may have caused this pigmentation

SWEATING A sweating crisis occurring with an exacerbation of pruritus sometimes occurs according to Hallopeau and Jeanselme (145f) A patient who had absence of sweating was reported by Levin (208a) In this case it was not possible to identify the sweat glands histologically although they had been demonstrated six months previously He believed this condition to be due to roentgenotherapy and not to mycosis fungoides Cannon (58a) was of the opinion that the absence of sweating was due to atrophy from roentgenotherapy since it had occurred in two of his patients following this treatment

6 *Mucous Membranes* Lesions of the mucous membranes are extremely rare but may occur in mycosis fungoides Wertheim and Smith (358) described a patient whose tongue was bulky and indurated the gums swollen and the hard and soft palates infiltrated and ulcerated Berggreen (27) in a study of 48 patients having mycosis fungoides found three to have mucous membrane involvement White patches and superficial ulcers affecting the tongue buccal and pharyngeal mucous membranes were described by Hallopeau and Weil (145m) A patient having similar lesions who was unable to ingest solid food because of pain of the buccal cavity and tongue was reported by Sequeira (311b) A patient having progressive gangrene of the hard palate was described by Hallopeau and Jeanselme (145g) Breakey's (47) patient had deposits in the tongue tonsil and in the viscera Oral involvement was also reported by Curtis *et al* (73b)

The tonsils may be tumorous or diffusely hypertrophied A tumor of the supratonsillar fossa was reported by Hallopeau and Jeanselme (145i) A woman who had difficulty in swallowing because of a small rounded tumor on the free edge of

the reticuloendothelial response is diffused and the infiltrate more polymorphic in the lymphomas The diagnosis in their case was based on the widespread intense reticulosis marked polymorphic cellular infiltrate clumping of endothelial cells and the presence of Pautrier's abscesses The numerous polymorphonuclear eosinophils and fewer mononuclear eosinophils was not characteristic but the histologic features were typical of mycosis fungoides

2) *Monocytosis* The peripheral blood monocytosis was believed by Montgomery (245c) to be suggestive of a reticuloendothelial origin of mycosis fungoides Kindler (183) reported a patient having 27 per cent monocytes He did not believe this finding to be uncommon since up to 60 per cent monocytosis has been recorded

3) *Lymphocytosis* Peripheral blood lymphocytosis may be a terminal manifestation of mycosis fungoides A patient having 51 per cent lymphocytes in the peripheral blood was described by Woringer and Renard (371b) The lymphocyte count decreased and the cutaneous eruption improved following roentgenotherapy Duverne *et al* (94) described a patient who had a premycotic erythema for which arsenic and roentgenotherapy were administered A fatal agranulocytosis developed following treatment and could not be controlled by massive doses of penicillin

b Bone Marrow The bone marrow changes in 11 patients having various stages of mycosis fungoides were reported by Lapière and De Weerdt (197d) who found the bone marrow to have a reticuloendothelial reaction The percentage of reticuloendothelial cells monoblasts lymphocytes and plasma cells varied from *five to ten* In four cases they exceeded 10 per cent while there were 20 per cent the highest count in one case Santoianni (302) described similar findings in four cases Lapière and De Weerdt reported hyperplasia of the erythrocytes which they believed were due to cutaneous toxins in two of 11 cases of mycosis fungoides One of their patients exhibited a slight inhibition of maturation of neutrophilic granulocytes An increase of eosinophils in the sternal

tioned peripheral blood eosinophils, we found the average incidence to be from 4 to 9 per cent

Eosinophilia is a frequent occurrence in cutaneous diseases associated with severe pruritus It occurs in about 15 per cent of Hodgkin's disease patients and is frequently persistent in

TABLE VII

PERIPHERAL BLOOD EOSINOPHILIA

(*Average*)

Type	*Per Cent Eosinophils*
Classical	9 32
"D Emblee"	4 19
"Erythroderma	6 40

pemphigus and dermatitis herpetiformis Wintrobe (366) stated that the degree of eosinophilia parallels the extent of cutaneous involvement in any disease However, the significance of peripheral blood eosinophilia in any cutaneous disease is not known, according to Weidman (352a) and Lewis and Cormia (210)

Cutaneous granulomas having high tissue eosinophilia and reticuloendotheliosis were designated by Weidman (352a) as eosinophilic granuloma of the skin" which he subdivided into idiopathic and symptomatic the latter denoting the new entity In the idiopathic group, it is well known that there may be a high tissue eosinophilia in Hodgkin's disease, and there may be a high peripheral blood eosinophilia in mycosis fungoides according to L McCarthy (224a)

Irgang and Ultmann (165) described a 45 year old Negro who had both tissue and peripheral blood eosinophilia He had a generalized, moderately pruritic, cutaneous eruption for four years and 58 per cent peripheral blood eosinophilia They stated that either lymphoma or eosinophilic granuloma of the skin should be considered in patients having tissue eosinophilia with a reticuloendothelial reaction The reticulosis is localized and perivascular in eosinophilic granuloma of the skin while

the reticuloendothelial response is diffused and the infiltrate more polymorphic in the lymphomas The diagnosis in their case was based on the widespread intense reticulosis marked polymorphic cellular infiltrate clumping of endothelial cells and the presence of Pautrier s abscesses The numerous poly morphonuclear eosinophils and fewer mononuclear eosinophils was not characteristic but the histologic features were typical of mycosis fungoides

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59 Mycosis fungoides (clinical diagnosis) Bronchogenic carcinoma found at autopsy

bone marrow with or without peripheral blood eosinophilia was also noted They had observed this disassociation between blood and sternal bone marrow in Hodgkin s disease Their conclusion was that the reticuloendothelial reaction of the sternal bone marrow was typical in mycosis fungoides although this reaction was not consistent and until proved that it exists only in mycosis fungoides should not be considered specific for this disease They also noted an inconstant eosinophilia or with blood eosinophilia an inhibition in the transformation of metamyelocytes to neutrophilic leukocytes and disturbances in the maturation of red blood cells

A high proportion of reticuloendothelial system cells and a few histiocytes characteristic of mycosis fungoides were present in six of the cases reported by Tzanck *et al* (342) However Lapiere and De Weerdt (197d) were unable to demon



60 Mycosis fungoides (clinical diagnosis) Bronchogenic carcinoma found at autopsy

strate these histiocytes in studying bone marrow smears in six cases They concluded that 1) they were unable to confirm the presence of a reticuloendothelial reaction 2) there was a slight increase in eosinophilia 3) although present in some cases the eosinophilia was not persistent 4) several cases showed degenerative and abnormal lymphocytic cells and 5) the changes observed were not specific for mycosis fungoides

According to the present consensus the bone marrow does not reveal a specific picture of mycosis fungoides according to Tilley and Smith (335)

c BIOCHEMICAL EXAMINATIONS In studying the blood protein levels of mycosis fungoides patients, Amorati *et al* (3) found the albumin-globulin ratio to be fairly high as a result of hyperalbuminemia and hypoglobulinemia Among the separate globulin fractions, they found the gamma globulins to be increased while the alpha and beta globulins were frequently diminished

d BASAL METABOLIC RATE The patient reported by Senear *et al* (310c) had a 35 plus basal metabolic rate Lynch (221) commented that this elevated metabolic rate is observed frequently in leukemia, sometimes as an early symptom

8. Allergy. According to Rosenthal (297), approximately 80 per cent of mycosis fungoides patients have a positive tuberculin allergy reaction A more detailed discussion of this allergic aspect is included in Chapter IV

B The "Erythroderma" Form

This condition is sometimes described as the "homme rouge" or femme rouge' stage of mycosis fungoides This so called "erythroderma,' or diffuse form of mycosis fungoides was first described by Hallopeau and Besnier (145c) The symptoms, entirely different from those of classical mycosis fungoides consist of an uncharacteristic, universal exfoliative dermatitis occurring as the only manifestation of the disease This eruption is frequently preceded by pruritus, it develops rapidly on previously normal skin and eventuates in tumor formation However, we believe that, histopathologically these cases are either lymphocytic leukemia, Hodgkin's disease, reticulum cell lymphosarcoma or some other form of malignancy, and are not mycosis fungoides

The erythroderma is associated with peeling of the skin and varies from bran like scales to large lamellar flakes according to Poulsen (278) There is usually severe pruritus and thickening of the skin causing formation of large folds resulting from diffuse cutaneous infiltration which is particularly marked on the trunk (cutis laxa) Because of the intense pruritus and

underlying systemic pathology lymphadenopathy is frequent and the course is rapidly fatal

The lesions were described by Sequeira (311b) as red or violet colored dry plaques which occasionally develop into fine scales and primarily involve the flexures although universal involvement may occur Trophic changes such as alopecia of the affected areas and nail involvement may occur when cutaneous edema and lymphadenopathy are present Superficial ulcers and "white patches" may occasionally involve the lips and buccal mucosa Nodules and tumors subsequently develop but the characteristic tumors have not always appeared at the time of death in some cases

Although the "erythroderma" type may precede the development of tumors by several years it may also follow their appearance according to Hallopeau and Besnier (145c) Usually there is a gradual generalization of the eruption and there is normal skin between the cutaneous folds as well as thickening of the skin which is coincident with the erythema In some areas the eruption may be papular it may be pigmented there may be a hair in the center of each papule or it may be centrally depressed They described the eruption as always severely pruritic and marked scratching causing excoriations and ecchymoses result in lymphadenopathy The erythroderma may improve leaving areas of pale skin There is occasionally pallor in the axillary and nipple areas or triangular areas of normal skin may be present

Lapiere (197a) described two forms of this "erythroderma" type The acute form lasting from three to five years eventuates in the chronic form in which cachexia develops This acute form consists of generalized pruritus followed by erythematous scaling which is at first superficial but later becomes infiltrated resulting in generalized erythroderma The pruritus increases in severity and a primary plaque described as the "chancre inoculation of Hallopeau" may occasionally precede the erythroderma In the chronic form there is a generalized erythroderma and areas of normal skin are seldom present The skin is dark red to violet in color which becomes

more intense during periods of crises when pruritus sweating and chills occur, as well as fever, lasting for several hours which may appear several times daily for a number of days The fever then subsides the disease becomes inactive and abundant laminated desquamation occurs

In certain areas the cutaneous nodules may be palpable a factor which Wickham (361) considered pathognomonic of the disease The cutaneous folds and ridges caused by the infiltration are not present in other erythrodermas according to Besnier (31a) and Brocq (48a)

The characteristic picture of facial involvement consists of large almost leonine features and occasionally a "drawn" look resulting in a mask like appearance An ectropion appearance may result from retraction of the eyelids and the conjunctivae may be injected The scalp and body hair may disappear almost completely while the remaining hair is broken and brittle The palms and soles are hyperkeratotic Scratching results in ulceration and secondary infection although no visible scratch marks are apparent Superficial lymphadenopathy occurs in the terminal stage of the disease and tumors may appear Although the absence of pruritus appears to be rare in this form of the disease Rosenthal (297) described a patient who did not have pruritus

A 48 year old woman who had an initial erythroderma and well defined atrophic evolution in some cutaneous areas was described by Watrin (350) A 66 year old man who presented a nonpruritic generalized premycotic erythroderma which tended to become atrophic and form nodules at the onset was reported by Gougerot and Blum (139b)

A patient having lymphadenotic erythroderma (diffuse lymphadenosis of the skin) was described by Arndt (6a c) Histologically the infiltration which was purely lymphocytic involved the middle and lower dermis Except for dilated blood vessels and edema of the papillary portion of the corium these areas appeared to be normal

The histologic picture may vary according to the specific disease present Changes found in Hodgkin s disease lympho

cytic leukemia or lymphosarcoma *may be present* However a few general observations concerning this condition would include the following Changes consisting of a continuous diffuse more or less circumscribed infiltration may be found in the upper layers of the dermis papillae and subpapillary portion of the corium The blood vessels are dilated and the cellular infiltration is composed of lymphocytes proliferated connective tissue cells mast cells and pigment cells while plasma cells are not present

Patients having the characteristic symptoms of this condition have also been described by Barber (14) Davis (76) Finnerud (105a) Howard Fox (112c) Tilbury Fox (113) Graham Little (140) Hughes (161) Kogoj (188) Mac Kay and Boyd (227) Oliver (259b) Sibley (316) and Wise (368e)

C Tumor "D Emblee" Type

This form of the disease which we believe to be lymphosarcoma rather than mycosis fungoides was first described by Vidal and Brocq (346c) Among 40 case reports having adequate data we found 33 patients were men and seven were

TABLE VIII

Sites of Involvement of Mycosis Fungoides D Emblee

Site	*Number of Cases*	*Total Cases*
Head		15
Face	8	
Scalp	7	
Trunk		5
Chest	2	
Groin	1	
Axillary fold	1	
Abdomen	1	
Back predominantly scapular area	6	6
Extremities		1
Upper	7	
Lower	8	
Buttocks	[illegible]	

women The average age of the men was 60 years and 62 years in women The youngest men, both 32 years of age, were reported by Iclaramunt (163) and Audry (10) The oldest man 83 years of age, was described by Wills (363b) The women were from 56 to 66 years of age However, three very young patients have been reported An eight month old girl who developed tumors "d'emblee" during the first few days of life was described by Serra *et al* (313). A 12 year old girl who had paraplegia due to a tumor in the dorsolumbar region, involving the spine, was reported by Decrop *et al* (78b), and Sereni's (312) patient was a 16 year old girl who died two and one-half years after she developed the 'd'emblee" form

Sites of Involvement. The areas of involvement, in order of frequency, appear to be the extremities, head, back and trunk

Trauma. Some degree of trauma has frequently been described in the "d'emblee" form The development of this condition following an insect bite was reported by Livingood and Scully (214a) A 39 year old man who was bitten by an insect on the dorsal surface of the right forearm was described by Eller and Rein (98b) This area, which was intensely pruritic was scratched continually and became inflammed and edematous within a few days A circumscribed, indurated, painful 7 by 6 cm tumor, then appeared in this area and was considered to be a "carbuncle" The lesion was incised but contained no pus and the tumor was then removed three weeks later Histologic examination revealed a chronic, suppurative inflammatory reaction and infiltration of the cutis and subcutis with polymorphonuclear leukocytes and round cells Three weeks later a nonpruritic eruption appeared on the face and became generalized within two days There were numerous, bright red, soft, 5 by 15 mm papules and nodules involving the face and neck and a 9 by 11 cm ulcerated, granulomatous lesion, which extended down to the muscle involving the right forearm It was stated, however, that the insect bite may have been coincidental to the development of the "d'emblee" tumor

Among the many reports of the "d'emblee" form following

injury were two cases described by Fraser (114b) The first patient (case 1) was a 58 year old woman who had injured her leg six or seven years previously The leg became edematous one month after this injury and numerous brown macules and small nodules appeared on various cutaneous surfaces of the body These lesions disappeared and recurred during the following two years when they began to increase in size and some ulcerated Histologic studies of the cutaneous tumors tonsils mesentery omentum kidney capsules and mesenteric and bronchial lymph nodes at autopsy all revealed typical lymphosarcoma The second patient (case 3) a 42 year old man had injured his wrist seven years previously During the succeeding years this same area had been injured repeatedly and the skin became rough scaly and markedly pruritic A 2 cm warty growth raised 5 mms above the surface of the skin then developed above the volar aspect of the left wrist Histologic examination was suggestive of mycosis fungoides but examination of the entire lesion revealed lymphosarcoma

The patient described by Crocker (71 a) had received a knee injury which resulted in prolonged suppuration of the head of the tibia He then developed lesions of mycosis fungoides on the scalp and upper chest Mc Vail *et al* (225) reported a 43 year old man who received a bruise in the right temporal region which continued to increase in size Several weeks later tumors appeared at the vertex of the scalp and over the parietal bone Eventually the entire body became involved with tumors and he died A 48 year old man who had received a long deep scalp wound was presented by Sequeira (311b) A nodule which grew to walnut" size during the next 15 months soon appeared at the site of injury One year later the entire scalp was covered with tumors There was an 8 by 10 5 cms granulating tumor at the vertex of the scalp and various sized ulcerating fungating tumors involved the chest and back There had been no evidence of a premycotic eruption in this case

Riecke (292) described a 53 year old man who had injured

women The average age of the men was 60 years and 62 years in women The youngest men, both 32 years of age, were reported by Iclaramunt (163) and Audry (10) The oldest man 83 years of age, was described by Wills (363b) The women were from 56 to 66 years of age However, three very young patients have been reported An eight month old girl who developed tumors "d emblee" during the first few days of life was described by Serra *et al* (313) A 12 year old girl who had paraplegia due to a tumor in the dorsolumbar region involving the spine, was reported by Decrop *et al* (78b) and Sereni's (312) patient was a 16 year old girl who died two and one half years after she developed the "d'emblee" form

Sites of Involvement The areas of involvement in order of frequency, appear to be the extremities head, back and trunk

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Among the many reports of the 'd emblee" form following

rapidly" As early as 1900 Brocq (48a) stated that this "d emblee" type is closely related to lymphosarcoma of the skin

Eosinophilia is usually present in this form of the disease which has no premonitory signs or symptoms Pruritus usually occurs and one or several tumors develop on apparently normal skin Poulsen (278) believed that these primary" tumors were more stable and circumscribed and tended to ulcerate in contrast to the mycotic tumors which appear in the terminal stages of classical mycosis fungoides A single tumor may be the sole manifestation of the "d emblee" type for many years or occasionally throughout life

However since these cases described as mycosis fungoides "d emblee" are actually a localized form of lymphosarcoma they should be so designated and not be included with mycosis fungoides an opinion shared by Fraser (114b) Montgomery (245c) and Oliver (259a) All six cases of the "d emblee" form studied by Fuhs (116) proved to have the histologic structure of lymphosarcoma and Favre (102) stated that all cases of this type which he had studied showed a lymphosarcomatous structure

Andrews (4) described a 74 year old man who developed a 7.5 cm cutaneous lesion in the lower left abdominal quadrant This lesion healed completely following roentgenotherapy but nine years later a pruritic eruption consisting of erythematous psoriasiform infiltrated patches appeared on the legs and thighs An 80 year old man reported by Dore (86a) first developed a "carbuncle" which was followed by a cutaneous eruption involving the trunk and extremities This eruption had been present for one year and Dore believed the original lesion was a mycotic tumor preceding the cutaneous lesions A 44 year old man who developed tumors prior to the premycotic eruption was described by Dubreuilh (90) He first developed a small crusted cutaneous plaque on the eyelid and three months later a weeping crusted, pruritic eruption appeared in the axilla nose and upper lip Bennett (25) reported a 59 year old man who had injured his leg five years previously

the back of his head. A plum sized swelling occurred which gradually became firm, elastic and livid red in color and caused alopecia in this area. This lesion, which increased to "palm" size, was depressed in the center and covered with brown scales but did not ulcerate. The mucous membranes were also involved and ulcerating tumors were present on the hard palate. Autopsy disclosed lesions in the dura mater, kidney, adrenal glands and retroperitoneal lymph nodes which showed the same histologic structure as the scalp tumors.

Clinical Features. The characteristic features of the d'emblée form were described by Vidal and Brocq (346c) in 1885. They stated: The lesions are much more circumscribed, do not have the characteristics of the preceding types, never are generalized; if they are multiple, form sometimes one or more tumors which are well defined and of a fixed character. One does not observe the premycotic or infiltrative stage. This form is a much more grave type and cases end fatally very



61. Mycosis fungoides d'emblée proved to be lymphosarcoma.





64 Mycosis fungoides d'emblee proved to be lymphosarcoma
65 Mycosis fungoides d'emblee proved to be lymphosarcoma

Although this lesion healed well a raised red lesion appeared at the same site six months later Erythematous lesions having slightly raised borders and atrophic centers subsequently appeared and there was a large fungating necrotic ulcer on the left thigh Graham Little (140) and Weissenbach *et al* (355) have described similar cases





62 Mycosis fungoides d'emblee proved to be lymphosarcoma

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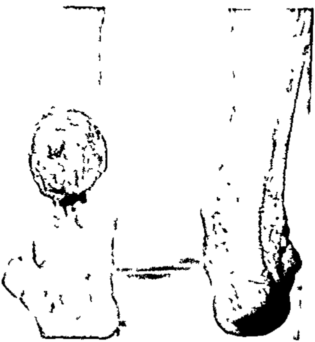




64 Mycosis fungoides d'emblee proved to be lymphosarcoma
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(Bluefarb and Schwartz *Arch Dermat* Feb 1956)

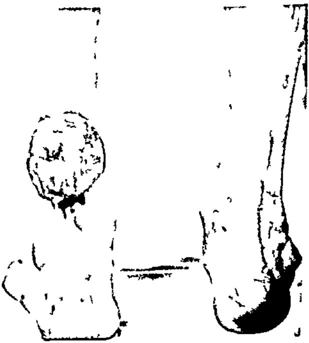
There are reports of an unusual type of the tumor "d emblee" form in which there was a successive and rapid development of multiple infiltrated plaques that soon developed into tumors which became more numerous than the infiltrated lesions This uncommon type was described by Cornbleet (67a) in a 74 year old man who had no premycotic lesions or pruritus He first developed mushrooming tumors on the right wrist and posterior hair line and several various sized sharply outlined infiltrated plaques with beginning tumor development appeared near the scalp lesion and on the left ear lobe

The appearance of a solitary tumor which increases in size and becomes ulcerated appears to be the most frequent "d emblee" form described Similar tumors usually appear some weeks or months after the original lesion The following case is illustrative of this form

> *Case Report* (See Illustration 42) A 44 year old woman first developed a cutaneous lesion on the left flank which increased to 10 by 18 cms in size during the following eight months A tumor then developed on the right flank and a satellite lesion appeared on the left flank These nonpruritic lesions were erythematous nodular and tended to ulcerate In some areas the border of the lesion was *serpiginous* and some lesions tended to heal spontaneously

Hallopeau and Leredde (145j) described the primary or initial lesion of mycosis fungoides as the chancre of the disease comparable to the primary lesion of syphilis" A 32 year old man who had developed a small tumor on the back six months previously was described by Audry (10) The tumor was excised and there had been no recurrence nearly four years later The "chancre" of mycosis fungoides is usually a discrete lesion but surgical excision is not always curative A patient described by Dore (86b) had excision of the primary lesion but mycosis fungoides occurred 20 years later Bamber (13) reported a 66 year old woman who first developed a "lump" on the buttock which was excised Ten years later a larger round firm pink tumor which occurred adjacent to the scar from the





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36 year old man who first developed a "boil like" lesion in the left groin six or eight weeks previously This lesion grew to "plum" size and was followed by a generalized cutaneous eruption consisting of nearly circular tumors Another patient (276 case 2) a 17 year old boy had a cutaneous nodule over the upper end of the sternum of one months duration This lesion was at first pink in color but one week later the color deepened and the size increased At this time similar non pruritic painless nodules began to develop on all areas of the body except the scalp arms and soles and underwent the same changes as the original sternal tumor The lesions were most numerous on the chest and lower abdomen with a few on the legs and he showed marked dyspnea A 63 year old man who had a 4 cms raised ulcerated lesion at the base of the right thumb of three months duration was reported by Cipollaro (64) This lesion disappeared following roentgenotherapy but scaly erythematous and infiltrated patches developed in various areas particularly on the hands forearms feet and legs five weeks later Price (279) presented a 39 year old man who had painful erythematous fluctuating edema of the dorsal surface of the right forearm for two months The lesion was considered to be a "carbuncle" but incision revealed it to be fibrotic This wound ulcerated and a generalized erythematous eruption consisting of "split pea" to "walnut" sized nodules developed Histologic studies of these nodules and the original tumor revealed lymphosarcoma A similar case in which the lesions were localized to one foot was described by Senear (310i) and Hallopeau and Damville (145e) reported a patient with cutaneous tumors involving only the face and ears Hallopeau and Roché s (1451) patient had tumor formation involving almost the entire face and to some extent the scalp in addition to an eczematoid dermatitis of one hand Three patients who had cutaneous involvement limited to the legs as well as atypical manifestations of the disease were reported by Oliver 259i A 65 year old man described by Bruchet (49) first developed a subcutaneous nodule on the hip followed by simi

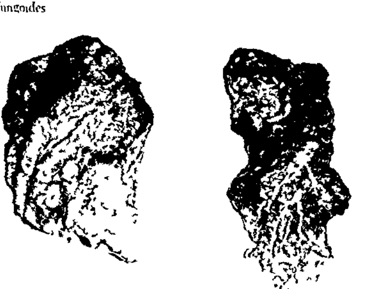
previous lesion, appeared A woman, described by Evans *et al* (99), developed marked enlargement of both breasts which were of a "doughy" consistency The skin of the right breast appeared to have "diffuse carcinomatous involvement" and was of an orange red color A 56 year old woman reported by Pautrier and Woringer (268g), developed the primary lesion on the chin and Iclaramunt (163) described a 32 year old man who had a solitary tumor on the chest which had been present for six months

A 38 year old man who had no evidence of a pruritic dermatitis prior to the development of a "pea' sized, bluish nodule on the back, was described by Wile (362a) This lesion, present for 14 months, had grown rapidly and several smaller lesions appeared in the surrounding cutaneous areas Sweitzer (330) described a 69 year old man who had several painless ulcerated cutaneous nodules on the anterior surface of the left thigh which had been present for one year A 60 year old patient reported by Basu *et al* (16), had developed a nodular lesion in the right palm two years previously The lesions then became generalized and ulceration of the right tonsil occurred However, histologic examination of the lesions revealed lymphosarcoma Quero (282) described a Negro who had numerous fungoid tumors of the scalp face, neck, trunk and extremities, which had begun as a tumor "d emblee" seven years before A 72 year old man who first developed an ulcerated tumor of the right thigh was reported by Bouvier *et al* (42) This tumor regressed spontaneously but another deep hypodermic tumor developed at the border of this tumor and still another, having a fungoid center, appeared later Small discrete, noninfiltrated, nonpruritic, parakeratotic plaques appeared around the umbilical plaque and evolved into tumors within a few days time Radiculitis of the dorsal area and a flaccid paraplegia occurred before death At autopsy, an extradural tumor, which compressed the bone marrow, was found to have similar histologic characteristics to the cutaneous tumor on the thigh Portnov (276 case 1) described a

skin in eight of 10 cases in which autopsy was performed

Occasionally visceral lesions are detected during life Although they rarely cause symptoms there may be albuminuria obstructive jaundice (as described by Goldsmith 1361), discomfort resulting from hepatomegaly or splenomegaly or tumors of the mouth which interfere with digestion and speech However, these are rare *clinical complications*

These conclusions however are mainly true for the "erythroderma" and d emblee" forms This involvement is not common although it may occur in classical (Alibert) mycosis fungoides



65 Nodules throughout the lungs

1 Lymph Nodes Lymphadenopathy is reported to occur in about 50 per cent of all cases of mycosis fungoides The lymph nodes are firm elastic indolent and freely movable with a normal overlying skin

Both theories that have been advanced regarding this lymph node involvement are probably correct The first attributes the

lar nodules involving the hip and achilles tendon of the right leg Similar cases have been reported by Besnier and Hallopeau (31b), Kreibich (191), Malherbe (230), O'Donovan (256a) and Strobel and Hazen (326)

D. Internal Organ Involvement

All cases having internal organ involvement reported up to 1909 were reviewed by Paltauf (265b) He concluded that internal organ involvement is rare and this view is concurred by others, including Ormsby *et al* (261c), Montgomery (245a), Mac Leod (229) and Unna (344) However, Liechti (211) collected 22 authentic cases of internal organ involvement which were reported from 1895 to 1927, and added two additional cases He concluded that Paltauf's dictum was erroneous This again proves that a difference of opinion is due to the fact that no distinction was made between the various types of the disease Faber (101) reported a case of internal organ involvement without cutaneous lesions

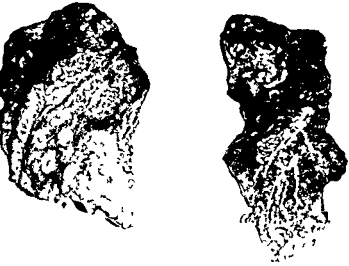
Among 42 cases reported between 1928 and 1938, Berman (29) found 18 listed complete autopsy findings Of these, 16 patients had internal organ involvement, while in one case this involvement was not determined and in another it was not given He found the spleen, liver and lungs to be the organs most frequently involved, while there was intestinal involvement in five, and adrenal gland involvement in four cases Berman concluded that internal organ involvement is the rule rather than the exception, and the prevailing opinion that such involvement is rare is based upon incomplete evidence

Visceral manifestations are usually described in the "erythroderma" and "d'emblee" cases which come to autopsy The skin and lymph nodes are most often involved, with the lungs, liver and spleen next in frequency There is less frequent involvement of the intestines, adrenal glands, testes and nervous system, while involvement of the tonsils, pancreas, kidneys pharynx, parotid gland and heart is rare Curtis *et al* (73b) found involvement of structures other than the

skin in eight of 10 cases in which autopsy was performed

Occasionally visceral lesions are detected during life. Although they rarely cause symptoms, there may be albuminuria, obstructive jaundice (as described by Goldsmith 136a), discomfort resulting from hepatomegaly or splenomegaly, or tumors of the mouth which interfere with digestion and speech. However, these are rare clinical complications.

These conclusions, however, are mainly true for the "erythroderma" and "d'emblee" forms. This involvement is not common, although it may occur in classical (Alibert) mycosis fungoides.



68 Nodules throughout the lungs

1. Lymph Nodes. Lymphadenopathy is reported to occur in about 50 per cent of all cases of mycosis fungoides. The lymph nodes are firm, elastic, indolent, and freely movable with a normal overlying skin.

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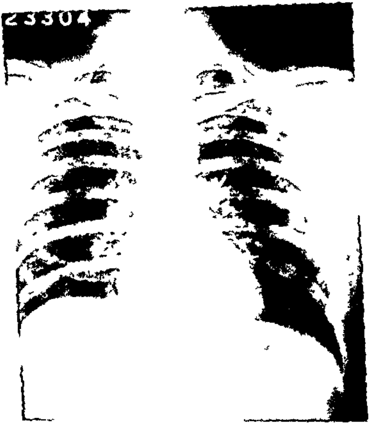
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bronchopneumonia or lymphangitis carcinomatose These changes are characteristic in that apices remain free until the end markedly different than the picture seen in tuberculosis"



61 Hilar streakings in the lungs (Bluefarb and Steinberg Ann Int Med Feb 1952)

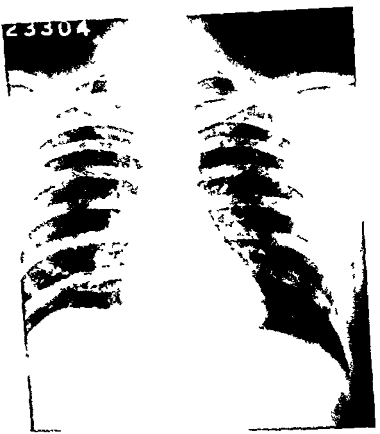
Detailed roentgenologic changes in mycosis fungoides were first described by Kuznitsky (182) who termed them "speckled streakings" or "stippled streakings He reported a patient who

regional lymphadenopathy to a simple hyperplasia resulting from secondary cutaneous changes and the second theory holds that the lymphadenopathy is independent of secondary cutaneous changes and should be interpreted as mycosis fungoides of the lymph nodes

Numerous cases having lymph node involvement have been described One patient, reported by Paltauf and Zumbusch (265e case 1) had inguinal and axillary lymphadenopathy and another (case 2) had cervical, bronchial, retroperitoneal and mesenteric lymphadenopathy as well as involvement of the nodes of the hilus of the liver and the spleen Eight of Berggreen's (27) 48 patients had lymph node involvement Other cases having this involvement were described by Bluefarb and Steinberg (38f), Breaky (47), Godel (131), Hallopeau and Jeanselme (145h), Hemmingson (152), Mac Kay and Boyd (227), Pautrier *et al* (268f), Post and Lincoln (277), Simek and Feuereisen (300), Wertheim and Smith (358), Zakon and Falkenstein (372) and Zinck (375)

2. *Lungs* The first report of lung involvement in mycosis fungoides was that of Breakey (47) in 1902 Werth (357) found that 31 cases of mycosis fungoides, in which chest roentgenogram findings were described, were reported up to 1940 The majority of these reports indicated merely "streaking" of accentuated hilar markings were present He described two additional patients in whom roentgenograms revealed enlargement of the hilar shadows with linear and spotty shadows extending from these regions into the lungs Reexamination, one year later revealed accentuation of these signs in both cases Because the picture resembled Boeck's sarcoid, tumor material was injected into guinea pigs and rabbits, but all results were negative Werth summarized the typical roentgenogram findings in mycosis fungoides as follows 'The lesions begin with hilar enlargement, which is not characteristic, followed by spreading of the affection along the blood vessels, and manifested roentgenologically by increased streakings Later tumorous changes occur small nodules appear along the vessels and bronchi so that the picture resembles

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69 Hilar "streakings in the lungs (Bluefarb and Steinberg *Ann Int Med* Feb 1952)

Detailed roentgenologic changes in mycosis fungoides were first described by Kuznitsky (192) who termed them speckled streakings" or "implied *streakings* " He reported a patient who

evidenced no clinical lung involvement but roentgenogram revealed changes similar to those which occur in Boeck's sarcoid Two other patients had marked lung involvement In these cases, there was a shadow over the lung area and there was accentuation of the bronchial tube shadows The apices were clear and there was no evidence of inflammatory change The von Pirquet test was negative Greifenstein's (142) report represents the most complete description of roentgenogram findings published up to 1937 His case was the first published with roentgenograms and the changes were described as "Many almost round coarsely speckled shadows," and these findings were confirmed at autopsy Two patients who had extensive visceral involvement were described in a detailed report by Paltauf and Zumbusch (265e) Mycosis fungoides tumors were present in the lungs in both patients Kovacs (190) described an 18 year old girl who developed mycosis fungoides at 11 years of age In addition to severe cutaneous involvement, there were typical lesions in both lungs These lesions were present on roentgenograms five months before death and the diagnosis was confirmed at autopsy

Among 48 cases of mycosis fungoides, Berggreen (27) found two having pleural involvement and two with lung involvement A patient who had mycosis fungoides with metastases as polymorphous cell sarcoma and lung involvement, was reported by Hemmingson (152) Arzt's (7b) patient presented pulmonary manifestations on roentgenograms which were interpreted as mycosis fungoides nodules A 17 year old boy who developed a cutaneous nodule over the upper part of the sternum one month previously, was reported by Portnoy (276) This lesion was at first pink in color but one week later the color deepened and it increased in size Similar lesions which underwent the same changes, appeared over the entire body except for the arms, scalp and soles Masses which were demonstrated in the lungs were presumed to be secondary deposits The disease, in this case, ran a rapidly fatal course

Howles and Connell's (158) patient had diffusely distributed nodules on the surfaces of both lung lobes The larger nodules,

4 cms in diameter were deep red in color vascular and very friable Histologic examination at autopsy revealed the lung and cutaneous lesions to have identical structure The nodular formation which invaded the lungs did not cause complete destruction of the alveolar wall such as that usually present in malignant growths but appeared to infiltrate and widen the interalveolar spaces Autopsy on Godels (131) patient a



70 Histological evidence of mycosis fungoides of the lungs (Bluefarb and Steinberg *Ann Int Med* Feb 1952)

39 year old man revealed mycotic lesions in the lungs pleura mediastinum tracheal mucosa epicardium soft palate skeletal muscles and lymph nodes Paltauf and Scherber (265d) described mycotic infiltration of the lungs heart walls of the stomach and uterus and right oculomotor trigeminal and femoral nerves in autopsy examination of a 30 year old woman Pulmonary involvement was also described by Curtis *et al*

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71 Nodular pulmonary infiltrates (Bluefarb and Steinberg Ann Int Med, Feb 1952)

72 Nodular pulmonary infiltrates

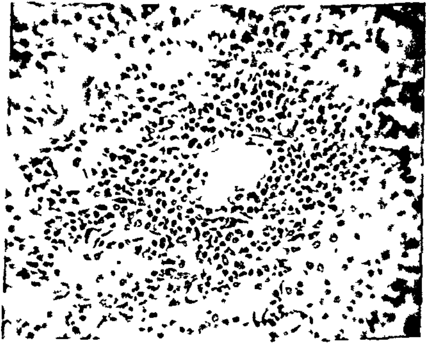
(73b) Cockerman and Montgomery (132) Goldsmith (136b) MacKay and Boyd (227) Post and Lincoln (277) Winer (365) and Zinck (375)

Roman (295) described a patient in whom histological examination of the lung nodules revealed the infiltrate to be so dense that the lung structure was not recognizable This case is similar to one described by Bluefarb and Steinberg (38f case 3) who reviewed the pulmonary manifestations of mycosis fungoides and described four patients having this involvement Their first patient a 54 year old man had cutaneous lesions for four or five years One week before death he developed progressive generalized jaundice cervical and axillary lymph adenopathy appeared diffuse subcutaneous hemorrhages most marked on the arms and forearms occurred and the scalp and eyebrow hair almost completely disappeared Roentgenogram of the chest revealed bilateral soft nodular infiltrates compatible with specific pulmonary infiltrates Autopsy revealed mycosis fungoides primary in the skin with involvement of the lungs liver testes stomach and bladder mucosa spleen pancreas and bone marrow The second patient a 58 year old man had a cutaneous eruption of 13 months duration Roentgenogram of the chest revealed pulmonary infiltration Autopsy disclosed generalized mycosis fungoides of the skin liver lung adrenal gland and lymph nodes as well as multiple benign polyposis of the descending colon and adenocarcinoma of the descending colon The third patient a 51 year old man had developed pruritus of the back 14 years previously Chest roentgenograms disclosed increased markings of the lung fields and increased infiltration of the pulmonary fields Autopsy revealed involvement of the lungs liver lymph nodes and skin The fourth patient a 33 year old man had psoriasis for 30 years Pigmentation and infiltrated plaques had appeared in the psoriatic lesions during the past 18 months Chest roentgenograms revealed increased density which was interpreted as possible mycosis fungoides infiltrates Marked improvement demonstrated roentgenologically occurred following nitrogen mustard and radioactive phosphorus therapy



71 Nodular pulmonary infiltrates (Bluefarb and Steinberg *Ann Int Med*, Feb 1952)
72 Nodular pulmonary infiltrates

Unna (344) found that the lungs while appearing normal macroscopically, showed marked perivascular changes on microscopic examination. He considered these changes to represent early mycosis fungoides and Bennek (24) confirmed this finding in other organs. These increased perivascular changes appear as "increased streakings" according to Werth (357). Perivascularity is the initial symptom of organic my-



73 Mycosis fungoides of the lungs (Bluefarb and Steinberg, *Ann Int Med*, Feb 1952)

cosis fungoides was first demonstrated by Paltauf (265c). It has been established that pulmonary involvement is invariably associated with generalized lymph node involvement. Therefore the path of infection may be assumed to be that the infectious agent enters the blood stream through either the skin, lungs or other organs and is retained in the lymph nodes

This infectious agent does not enter the lungs until there is a "breakdown" of the hilar lymph nodes These opinions are confirmed by the fact that all cases exhibit a clear hilar swelling and the apparent beginning of lung involvement is observed near the hilus according to Martenstein (235) The pulmonary involvement in mycosis fungoides closely parallels that observed in Boeck's sarcoid and there is a positive anergy to the tuberculin test in both diseases (See Immunologic Reactions Chapter IV)

3 Liver and Spleen There are numerous reports of involvement of both the liver and spleen occurring in mycosis fungoides as in the cases described by Bluefarb and Steinberg (38f case 1) Curtis *et al* (73b) Paltauf and Zumbusch (265e case 2) Samek and Feuereisen (300) Wertheim and Smith (358) and by Zakon and Falkenstein (372)

Patients having involvement of the liver were reported by Berggreen (27) Bluefarb and Steinberg (38f case 2) Curtis *et al* (73b), Godel (131 case 2) Hallopeau and Jeanselme (145h) Mac Kay and Boyd (227) Pautrier *et al* (268f) and by Winer (365 case 1)

4 Gastrointestinal Tract Although mucous membrane involvement is rare in mycosis fungoides such cases have occasionally been reported

Breakey (47) and Lausecker (200) described mycosis fungoides of the tongue and an illustration of this involvement appears in Mac Kee and Cipollaro's (228c) textbook Involvement of the tongue was reported by Curtis *et al* (73b)

The soft palate was involved in the cases reported by Auspitz (11) Curtis *et al* (73b) Godel (131 case 1) Hallopeau and Jeanselme (145h) and Poulsen (278) Involvement of the tonsil was described by Paltauf (265c) and Paltauf and Zumbusch (265e case 2)

Lausecker (200) and Post and Lincoln (277) reported involvement of the esophagus and the patients described by Goeckerman and Montgomery (132) Paltauf and Scherber (265d) and Paltauf and Zumbusch (265e case 1) had involve

ment of the stomach The patient reported by Roman (295) had a non-eroded infiltration of the gastric mucosa which was histologically identical to those present in the corium of the skin. Kaposi's (176b) patient had involvement of the duodenum. Weidmann (353) reported a patient who died from peritonitis following perforation of a mycosis fungoides lesion



74 Mycosis fungoides of the large intestine

of the stomach Branscheid (46) described a 30 year old man who developed mycosis fungoides lesions of the mouth, gums, tongue and larynx, although cutaneous lesions or pruritus never appeared The condition was believed to be "stomatitis ulcerosa" but, four years later, esophagoscopy disclosed three ulcers which had caused the retrosternal pain on swallowing, and the histology of these lesions suggested mycosis fungoides He also had maxillary lymphadenopathy At autopsy there was a large ulcer below the cardia and ulceration of the cecum

One of Bluefarb and Steinberg's (38f case 1) patients had in volvement of the stomach mucosa and large intestine In volvement of the pancreas and appendix was reported by Curtis *et al* (73b)

5 *Nervous System* A patient having lesions involving the grey and white matter of both cerebral hemispheres was de scribed by Breakey (47) Both Riecke (292) and Kobner (187b) reported involvement of the dura mater Meningeal involvement was described by Pautrier *et al* (268f) and in volvement of the choroid plexus by Hemmingson (152) Involvement of the right oculomotor trigeminal and femoral nerves was reported by Paltauf and Scherber (265d) The patient reported by Aub *et al* (9) had associated facial paraly sis and deafness

A 35 year old man who had involvement of the brain and cranial nerves was described by Moncorps and Borger (244) The cutaneous lesions had been present for six and one half months and the neurologic symptoms occurred five months later Symptoms referable to practically all cranial nerves as well as symptoms indicative of increased cranial pressure subsequently occurred Histologic studies at autopsy dis closed infiltrating cellular tissue similar to that of the cutaneous lesions present in the pia in the region of the corpora quad rigemina and left caudate nucleus in both gasserian ganglions and in all cranial nerves

Brandweiner's (44) patient was a 50 year old man who had mycosis fungoides for 30 years before he developed right sided hemiplegia His head and eyes deflected to the right but no Babinski sign was elicited and needle pricks were felt on both sides of the body Autopsy disclosed nodular masses of "hazel nut" to "apple" size distributed in the brain substance which were considered to be mycosis fungoides metastasis from the skin along the course of the blood vessels and therefore of hematogeneous origin The histologic structure of the brain tumors and cutaneous lesions was the same both having in filtration around the blood vessels Brandweiner believed the

absence of reticulum resulted from a separation of preexisting connective tissue fibers in the corium Curtis *et al* (73b) reported involvement of the dura mater

6. Kidneys. Kidney involvement has been reported by Curtis *et al* (73b), Goldsmith (136a), Pautrier *et al* (268f) Riecke (292) and Winer (365 case 1) Involvement of the cortex and medulla of both kidneys was described by MacKay and Boyd (227) Post and Lincoln (277) reported involvement of the left ureter and Paltauf's (265c) patient had involvement of the bladder One patient described by Bluefarb and Steinberg (38f case 1) and one reported by Curtis *et al* (73b), had involvement of the bladder mucosa

7. Heart and Great Vessels. Involvement of the heart occurred in the patients described by Arzt (7b case 1), Curtis *et al* (73b), Godel (131 case 1), Goldsmith (136a), Hemmingson (152), Paltauf and Scherber (265d), Pautrier *et al* (268f) and Zinck (375)

Paltauf and Zumbusch (265e) reported a patient who had *extensive visceral involvement, marked infiltration* of the blood vessel walls and a tendency toward early necrosis of the infiltrates Pautrier *et al* (268f) reported involvement of the walls of the blood vessels and heart involvement Curtis *et al* (73b) reported involvement of the aorta

8 Other Internal Organ Involvement. Patients having involvement of the testicles were described by Bluefarb and Steinberg (38f case 1), Chiale (63), Curtis *et al* (73b), and Paltauf and Scherber (265d) Involvement of the uterus was described by Paltauf and Scherber (265d) and of the vagina by Kobner (187b) and of the breasts by Goeckerman and Montgomery (132)

Bluefarb and Steinberg (38f case 2) Goldsmith (136a) Pye-Smith (281) and Zinck (375) have described involvement of the adrenal glands

Involvement of the skeletal musclature was reported by Curtis *et al* (73b) Godel (131) and of the iliopsoas muscle by Hemmingson (152) and Post and Lincoln (277) Kaposi (176b) and Paltauf (265c) described skeletal involvement

Curtis *et al* (73b) reported involvement of the diaphragm A patient having involvement of the pelvis with spontaneous fracture was described by Reich and Bonse (289b) There were areas of osteoporosis However histologic examination of a lymph node revealed reticulum cell sarcoma

A patient reported by Hemmingson (152) and one by Curtis *et al* (73b) had involvement of the thyroid gland and Bluefarb and Steinberg s (38f case 1) patient as well as one reported by Curtis *et al* (73b) had involvement of the bone marrow

E Association with Other Diseases

1 Carcinoma The association of carcinoma and lymphoma is not common and the simultaneous occurrence of carcinoma and mycosis fungoides is especially rare

Jordan and Areschewa (174) described 38 post mortem examinations of patients having mycosis fungoides and found no instance of associated carcinoma Prior to our report of two cases (Bluefarb *et al* 38d) we were able to find only eight previously reported cases having this association However since that time three additional cases have been described one by Garb and Fields (122c) one by Livingood *et al* (214b) and another by Brunsting *et al* (52)

The patient described by Garb and Fields (122c) was a 67 year old man who had mycosis fungoides for 31 years He then developed an ulcerated tumor above the right knee which was found to be a prickle cell epithelioma on histological examination The patient presented by Livingood *et al* (214b) was a 69 year old Negress who had a pruritic cutaneous eruption for 38 years She had developed an adenocarcinoma five years previously for which mastectomy was performed The following year the pruritus became severe and urethane [illegible] given T[illegible]
above th[illegible]
Two ye[illegible] cutaneous lesions consisted of scaly slightly infiltrated round and ovoid plaques involving the greater portion of the body particularly the trunk The patient pre

sented by Brunsting *et al* (52) was a 68 year old man who had mycosis fungoides adenocarcinoma and poikiloderma The mycosis fungoides of 51 years duration had appeared when he was 17 years of age The primary cutaneous lesion had occurred on the thigh and was present for ten years before the generalized dissemination with multiple lesions occurred At the age of 68 years surgery was performed for an adenocarcinoma of the rectal sigmoid At the time of presentation he also had poikiloderma Roentgenotherapy the only treatment he had received had been administered symptomatically when indicated Aub *et al* (9) described a patient who developed basal cell carcinomas epidermoid carcinoma and a temporary leukemia during the 14 years he had mycosis fungoides

Two cases of this association were described by Bluefarb *et al* (38d) The first patient a 42 year old woman first developed a cutaneous eruption five years previously which consisted of oval and round maculo papular squamous lesions which were discrete and sharply marginated and involved both breasts and buttocks A diagnosis of parapsoriasis was made and the eruption showed definite improvement following exposure to sunlight but never completely disappeared She was given neoarsphenamine mapharsen and bismuth injections for a 28 month period and 600 000 units of penicillin daily for ten days for late latent syphilis Six years later she received roentgenotherapy for carcinoma of the cervix Two years after this therapy she had developed two slightly elevated erythematous well demarcated soft slightly scaling lesions in the left axilla which were 3 by 5 and 1 5 by 2 5 cms in size There were oval slightly raised mildly erythematous soft finely scaling lesions 2 to 4 cms in size scattered over the trunk An irregularly shaped 8 cm lesion with slightly atrophic reticulated depigmentation and eczematous distal margins having crusted erosions was present on the medial aspect of the left leg and ankle An oval 4 by 6 cms erythematous slightly infiltrated lesion covered with loosely attached thin scales was present above the left malleolus Histologic examination of these cutaneous lesions revealed mycosis fun

goides The malignant cervical lesion had healed completely The second patient was a 58 year old man who had a generalized acute cutaneous eruption of 13 months' duration, and marked edema of the face and extremities Some of the lesions were superficial, erythematous, scaly plaques, some of which were infiltrated others were "rubbery," deep seated nodules, from 1 to 3 cms in size There was a generalized lymphadenopathy, most marked in the axillae He died 20 days after hospital admission The anatomical diagnoses, at autopsy, including histologic findings, were 1) generalized mycosis fungoides of the skin liver, lung adrenal gland and lymph nodes, 2) multiple benign polyposis of the descending colon, and 3) adenocarcinoma of the descending colon

After a thorough study of the literature, Beerman and Thomas (19) found that mycosis fungoides is very rarely associated with other diseases They described a Negress who was apparently in good health until seven years of age when she developed an acute episode of chills fever and coma which lasted for 12 hours and was followed by red scaly cutaneous lesions which first appeared on the face and later became generalized Scaling was most marked during cold weather and there were no remissions at any time She developed pleurisy at 14 years and pneumonia at 15 years of age When she was 32 years old a bilateral salpingo oophorectomy was performed because of a multilocular right ovarian cyst and two years later she developed a fetal adenoma of the right lobe of the thyroid gland with early hyperplastic goiter Three years later carcinoma of the uterine cavity was treated by amputation and irradiation but no recurrence was apparent 15 and 18 years later A diagnosis of congenital ichthyosiform erythroderma of Brocq was confirmed One year later a 12 pound uterine tumor was removed surgically Sixteen years later, she had developed verrucoid hyperkeratotic patches on the extremities and an indurated ulcerative lesion on the left side of the mouth which was associated with regional lymphadenopathy These lesions which had been present for two years were followed by similar ulcerative tumor masses involving the

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of the cervix may have induced the rectal lesion They had no evidence either for or against this possibility

The problem of multiple primary malignant tumors was surveyed in the study of Warren and Gates (348) However Beerman and Thomas (19) stated that no case like theirs was noted by these investigators nor did they offer any satisfactory explanation beyond so-called predisposition or susceptibility, to account for multiple tumors It is interesting that two to four per cent of all tumor patients are found to have multiple primary malignant tumors (two or more) of the same or different embryonal origin The question of whether the presence of one primary focus of cancer prevents or predisposes to another focus of malignancy has been the subject of much speculation Although some as Peller and Stephenson (270) believed that the intentional production of curable cutaneous carcinoma by irritations which are not carcinogenic to internal organs may prevent carcinoma of the internal organs others as Warren and Gates (348) cited convincing evidence that this is not always the case On the contrary cancer of the skin is more frequently associated with multiple cancer than would be expected on the basis of chance alone Beerman and Thomas (19) stated that although they could offer no real explanation for this finding it does however *suggest* the necessity for a complete survey of every patient presenting an established malignant lesion (e g of the skin) for other foci of neoplastic change (e g gastrointestinal tract genitourinary tract and other organs) This is merely emphasis of the dictum that a person with one embryonal or developmental defect is likely to possess others according to Beerman and Thomas

A 58 year old woman who had a cutaneous eruption of the breasts back chest upper abdomen and pubic region of three months duration was presented by Skeer (319) The eruption consisted of numerous round and oval erythematous lesions slightly infiltrated with fine scales and were of varying shades of red The histologic diagnosis was mycosis fungoides In addition she had diabetes mellitus generalized arteriosclerosis and carcinoma of the sigmoid colon near the

forehead and medial aspect of the left thigh and similar painful ulcers on the chin and upper lip Histologic examination of a lesion from the left side of the mouth revealed marked pseudoepitheliomatous hyperplasia near the margin of the ulcerated surface and a multiplicity of cell types in the corium The histologic features were those of mycosis fungoides However, it was not settled whether the congenital ichthyosiform erythroderma had been premycotic mycosis fungoides from the onset, since no histological studies had been done during this phase of the disease Subsequent histologic examination of a lesion from the forehead showed pseudoepitheliomatous hyperplasia and a multiform type of infiltrate in the corium with numerous eosinophils Three years later she had developed diarrhea and weight loss and a 10 cm, easily bleeding fungating "cauliflower-like" adenocarcinoma, which arose from the posterior rectal wall, was demonstrated on proctoscopic examination An abdominoperineal resection was done and a large locally extending carcinoma with extension to the perirectal lymph nodes was removed The following year she had developed swelling of the legs, particularly at night Histologic studies of the inguinal lymph nodes revealed proliferative endotheliosis but no carcinoma cells were noted and roentgenogram revealed metastatic infiltration of the lungs She then developed dyspnea, cough weakness and anorexia The inguinal lymph nodes and liver were palpable and there was a generalized scaly ichthyosiform cutaneous eruption She died of cardiac failure and autopsy revealed bilateral pleural effusion metastatic carcinoma of both lungs the liver and various lymph nodes Histologic examination of the skin disclosed a chronic dermatitis with hyperplasia of the epithelium and acute and chronic inflammation of the scalp, with ulceration These autopsy histologic sections were believed to show only inflammatory changes probably due to response to roentgenotherapy, and none of the characteristics of mycosis fungoides Beerman and Thomas stated that the successive occurrence of seemingly independent foci of carcinoma (cervix and rectum), in this case, raised the question of whether previous irradiation

Hughes (161) reported a 68 year old man who first developed red scaly patches on the front of the legs extending from just below the knees to 2.5 cms above the ankles. This eruption which was markedly pruritic gradually spread to the trunk, limbs, scalp and face so that six months later he appeared to have a severe exfoliative dermatitis. He was improved after one months hospitalization although the pruritus continued at night and the skin remained reddened with areas of small scaly patches on the trunk. Three months later he developed a nodule on the back of the left hand which was reported to be epithelioma on histological examination. Later subcutaneous nodules appeared on the backs of both hands and forearms which gradually increased to the size of "marbles." One month later the pruritus recurred but treatment with vitamins, antihistamines and a course of dimercaprol resulted in *improvement*. There was no longer scaling of the skin and the pruritus disappeared, although the redness and induration remained.

Jessner (173) described a patient having *mycosis fungoides* associated with carcinoma of the rectum. In reviewing 136 cases of mycosis fungoides reported in the literature, Jordan and Areschewa (174) found 38 cases terminated fatally. Death was due to cachexia in 10, probable roentgen ray damage in 10, metastases to internal organs in four, lung, heart, brain or endocrine gland complications in five, intercurrent disease in one and from unstated causes in eight cases. *It is noteworthy* that in none of these cases was carcinoma the cause of death. They (174, case 2) reported an 83 year old man who had a basal cell carcinoma and mycosis fungoides.

2. ***Lupus Erythematosus.*** The association of lupus erythematosus and mycosis fungoides has been described although this combination of diseases is unusual. Throne's (333) patient was a 43 year old woman who had lupus *erythematosus* for eight years and mycosis *fungoides* for three years. This association in a 54 year old man was reported by Becker (18) and Costello's (68) patient was also a 54 year *old* man. The woman described by Feit (104) had these two diseases for five and

splenic flexure with intussception The resected portion of the tumor revealed adenocarcinoma on histologic study

Among 13 patients reported by Poulsen (278), two had cutaneous carcinoma in addition to mycosis fungoides Hynes and Wintrup (160) reported squamous cell carcinoma of the face in a patient with mycosis fungoides Poikiloderma atrophicans vasculare with changes of mycosis fungoides, basal cell epithelioma and squamous cell epithelioma were present in a patient reported by Leavell *et al* (203)

Gold (133) reported a 75 year old man who had been under observation for 11 years He was originally treated for carcinoma of the scrotum by surgical excision and subsequently right inguinal lymphadenopathy was treated surgically and with deep roentgenotherapy There was no evidence of recurrence eight years later when left inguinal lymphadenopathy occurred but this did not prove to be carcinomatous However, one year later he developed a red cutaneous eruption on both legs which soon spread to involve the arms and back The involved areas bled freely with the slightest trauma This eruption had decreased somewhat in the year following onset and some previously involved cutaneous areas appeared normal At this time he presented symmetrical, well circumscribed deep red, nonindurated and slightly scaly plaques The lesions on the trunk were devoid of scales and there were areas of normal skin within the involved areas He had a marked radiodermatitis of the right inguinal region An area over the left forearm had not improved with superficial roentgenotherapy On histologic examination the epidermis showed loose hyperkeratosis and patchy parakeratosis with atrophy of the malpighian layer There was a dense infiltrate lying immediately under the epidermis and extending along the blood vessels consisting of large and small round cells plasma cells, polymorphonuclears and numerous mononuclears and polynuclear reticulum cells A few mitotic figures were present The stroma of the infiltrate was provided by argentophil fibers The histology was characteristic of mycosis fungoides

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one-half years Hallopeau (145b) presented a patient who first developed mycosis fungoides and one year later lupus erythematosus appeared

3. Addison's Disease. The association of mycosis fungoides and Addison's disease is apparently rare A 50 year old woman who had both these diseases was reported by Gerne (126) The lesions of mycosis fungoides had been present on the skin and mucous membranes for five years She had been treated with roentgen rays and urethane While receiving urethane therapy, acute Addison's disease developed which was assumed to be due to deposits of mycosis fungoides in the adrenal glands

4. Kaposi's Sarcoma (Multiple Idiopathic Hemorrhagic Sarcoma). There are few reports of the association of mycosis fungoides and Kaposi's sarcoma Winer (365 case 4) reported a 76 year old woman who had both diseases and Lapowski's (198b) patient had lesions of Kaposi's sarcoma on the toes and lesions of mycosis fungoides on the trunk

Lane and Greenwood (195b) described a patient who had typical mycosis fungoides Extensive roentgenotherapy was administered during the tumor stage Small, round, dome shaped, nonpigmented tumors then appeared on the feet These tumors grew rapidly in size and increased in number so that the toes were nearly indistinguishable before death These tumors gradually extended up the legs While early histologic studies of a nodule revealed mycosis fungoides, the histologic changes were later typical of Kaposi's sarcoma, with considerably less pigmentation than is ordinarily present Histologic sections, made at autopsy, disclosed the typical picture of mycosis fungoides at one end of a nodule while the other end revealed Kaposi's sarcoma

5. Leukemia The association of lymphocytic leukemia and mycosis fungoides was described by Gougerot *et al* (139e) and by Woringer and Malhuret (371a) Mycosis fungoides associated with *granulocytic leukemia* was *reported* by Hudelo *et al* (159)

6 *Deep Mycoses* The association of lymphomatous diseases and deep mycoses has been described under Hodgkin's disease (Chapter II)

Goldman (135b) stated that he had observed a man who had typical clinical mycosis fungoides characterized by chronic progressive cutaneous infiltration Histoplasmosis was demonstrated at autopsy and reexamination of the previous cutaneous histological sections revealed histoplasmosis A 46 year old man described by Garb and Miller (122d) had the tumor stage of mycosis fungoides Disseminated coccidiomycosis was demonstrated at autopsy They were able to find only two cases in the literature which were presumed to have this combination However Garb and Miller believed these cases described by Wernicke (356) and Zeisler (373) were compatible with coccidiomycosis resembling mycosis fungoides and not true examples of mycosis fungoides

7 *Psoriasis* (Psoriasis is discussed under Section F)

F Dermatoses Believed to Be Precursors of Mycosis Fungoides

The various dermatoses which have been reported to be precursors of mycosis fungoides include 1) psoriasis 2) parapsoriasis 3) poikiloderma atrophicans vasculare and 4) congenital icthyosiform erythroderma

1 Psoriasis Although all textbooks and monographs state that psoriasiform lesions may be prodromi of mycosis fungoides the question of whether psoriasis may be a precursor of mycosis fungoides is debatable

A patient having transformation of psoriasis into mycosis fungoides was reported by Howard Fox (112a) This patient had clinical psoriasis for 23 years when the character *of the eruption* changed and was proved to be mycosis fungoides Zumbusch (377) described a patient who had an eruption believed to be psoriasis for eight years which disappeared following chrysarobin therapy The *eruption recurred* later and was finally found to be mycosis fungoides Roman (295) reported a patient who had a cutaneous eruption of 15 years duration

diagnosed as "psoriasis," which cleared following local therapy Five years later a similar eruption appeared "which was again pronounced psoriasis and again treated as such until it almost completely disappeared" For the last six years of his illness cutaneous infiltrations and tumor formations appeared It was not stated whether the premycotic eruption was histologically diagnostic of psoriasis in any of these cases

A 60 year old man, reported by Wise (368c), had a widely disseminated generalized eruption of psoriasis which first appeared on the chest three years previously and then spread to involve nearly all parts of the body During a period of 30 years this eruption cleared almost entirely at times, but reappeared at intervals, and became widely disseminated 18 years after onset Following an attack of influenza seven years before, there was an almost complete remission which lasted for several months One year before the report, the cutaneous lesions became pronounced Traub (338b) commented that this patient probably had mycosis fungoides from the onset rather than psoriasis MacKee (228b) stated that he doubted whether a transformation from psoriasis into mycosis fungoides could occur, and it was well known that the prefungoid stages of mycosis fungoides may, for months or years, so closely resemble such diseases as psoriasis, parapsoriasis or clinical varieties of eczema that clinical or histological differentiation is not possible for long periods of time Schonberg (306) reported a patient who developed mycosis fungoides following generalized psoriasis of 34 years' duration Pruritus, not present previously developed after infiltrated plaques of mycosis fungoides appeared

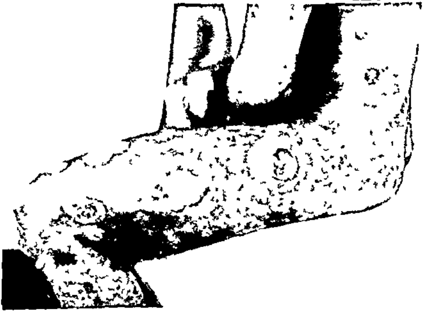
The literature on the simultaneous occurrence of psoriasis and mycosis fungoides was reviewed by Murphy and Montgomery (248) who found reports of two cases of histologically proved psoriasis preceding mycosis fungoides and they reported another case in which the definite histological diagnosis of psoriasis was made in an early stage of mycosis fungoides They assumed that their patient had psoriasis and mycosis fungoides concurrently but that the conditions were not re-

lated Since this report, Bluefarb and Ihrke (38c) reported a patient having both psoriasis and mycosis fungoides We are of the opinion that the psoriasis acted as a *locus minoris resistentiae* for the later development of mycosis fungoides In reviewing the literature, Murphy and Montgomery (248) found a lack of agreement as to whether psoriasis precedes mycosis fungoides Montgomery (245c) stated that eruptions resembling psoriasis may occur in the early stages of mycosis fungoides, as mentioned by Ormsby and Montgomery (261d), and that mycosis fungoides may begin with lesions indistinguishable from psoriasis, as stated by Sutton and Sutton, Jr (329) Herxheimer and Martin (154) stated "In a great number of cases the initial efflorescences of mycosis fungoides are morphologically so identical with psoriasis vulgaris that the diagnosis of psoriasis is made even in the presence of nodes and tumors because of the spectacular morphological analogy of the scaling lesions" There is almost universal agreement that prefungoid lesions often resemble psoriasis, as mentioned by Fraser (114a), Highman (156b), Lindenheim (213), Montgomery (245a), Thomson (332b) and Sulzberger and Wise (328) Most investigators include psoriasis in the differential diagnosis of premycotic eruptions There are three schools of thought at present 1) That psoriasiform premycotic lesions actually represent mycosis fungoides in its pre fungoid stage, no matter how closely they resemble psoriasis, clinically or histologically (MacKee 228b), 2) Mycosis fungoides and psoriasis may simultaneously exist in the same patient as separate diseases (Murphy and Montgomery 248, Bluefarb and Ihrke 38c), and 3) Psoriasis may develop into mycosis fungoides (Fraser 114d, Wise 368c)

The 33 year old man,* reported by Bluefarb and Ihrke (38c), had first developed psoriasis at three years of age During the previous four or five years ulcers had occasionally appeared in the psoriatic lesions Increased pigmentation of the entire body began to appear 18 months previously and a

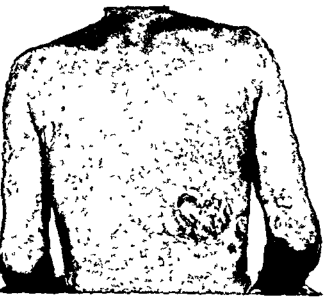
* See Illustrations 75 76 and 77





75 Psoriasis and mycosis fungoides in the same patient
76 Psoriasis and mycosis fungoides in the same patient (Bluefarb and Ihrke *N W Quart Bull*, 1952)

diagnosis of psoriasis was made Infiltrated plaques developed in the psoriatic lesions and the histologic examination revealed mycosis fungoides He was given nitrogen mustard therapy for three days but the condition did not improve Leukopenia developed and new fungating ulcerative lesions of mycosis fungoides continued to appear However, there was marked



77 Psoriasis and mycosis fungoides in the same patient

improvement with ultraviolet light therapy Numerous fungating ulcerative lesions of mycosis fungoides again developed and there was no improvement with adequate roentgenotherapy There had been a weight loss of 27 *pounds* during the past five weeks He had a cough with expectoration two months previously, which had cleared up after about one month as well as a peptic ulcer of three years' duration There was a generalized deep cutaneous pigmentation, somewhat mottled and with a bluish tinge but this pigmentation did not

differ on the exposed or covered parts of the body There were psoriasiform lesions with thin, silvery, loosely attached scales on an erythematous base, with little or no infiltration on the extremities and trunk which were not limited to the extensor surfaces and were from 2 to 8 cms in size On the forehead trunk and extremities there were 2 cm, circular, fungating lesions which had a keratotic surface On the shoulders sternocleidomastoid region, back, pelvis thighs knees and legs, particularly on the left hip and right forearm, were larger arciform, circinate, irregularly shaped, infiltrated areas some of which were ulcerated, exposing a purulent pink base These punched-out ulcers were sharply marginated and from 4 to 8 mms deep Examination of the lungs revealed soft coarse rales over the upper one third anteriorly and posteriorly Examination of the abdomen disclosed deep tenderness about the umbilicus There were varicosities of the right scrotum and of both legs Gastrointestinal roentgenogram disclosed an "Ulcer crater in the stomach," and the colon was reported as 'Spastic markedly contracted' Urine examination disclosed one to two red blood cells and six to ten white blood cells per high power magnification Treatment consisted of ACTH 25 mg four times a day for four days nitrogen mustard was given for four consecutive days one ampule in 500 cc saline This treatment produced nausea Two treatments with P 32 were given the first of four millicuries and the second of 4 29 millicuries The cutaneous lesions did not improve with this therapy Cortisone was administered for 14 days, beginning with 50 mg a day and increased until 200 mg a day was given on the last day This therapy was believed to have been of definite benefit to the cutaneous lesions and was supplemented by ultraviolet irradiation to selected areas all of which improved

Although the problem of the possibility of a transformation of psoriasis through a mycosis fungoides into a malignant reticulosis has not yet been clarified Degos *et al* (80) presented observations on a 61 year old woman whom, they believed presented further evidence in favor of such a transfor

mation. Murphy and Montgomery (248) stated that the rare coexistence of mycosis fungoides and psoriasis does not justify the assumption that true psoriasis is a precursor of mycosis fungoides. The following cases were regarded by the investigators, or their reviewers, to be mycosis fungoides preceded by true psoriasis.

TABLE IX

DURATION OF PSORIASIFORM ERUPTION PRIOR TO DIAGNOSIS OF MYCOSIS FUNGOIDES

	Case	*Age*	*Sex*	*Duration Years*
1	Abramowitz (1a) and Wise (1e)	51	F	11
2	Bluefarb and Ihrke (38c)	33	M	30
3	Degos *et al.* (80)	61	F	8
4	Fox, Howard (112a)	47	M	27
5	Fraser (114d)	29	F	3
6	Murphy and Montgomery (248)	26	F	12
7	Roman (295)	56	F	15
8	Rosen (296)	60	F	8
9	Schonberg (306)	45	M	34
10	Traub (338a)	44	M	10
11	Wise (368a)	50	F	15
12	(368b)	73	F	12
13	(368d)	50	F	15
14	(368i)	60	M	30
15	Zumbusch (377)	50	M	8
		Average Duration		15.9 Years

2. *Parapsoriasis*. As with psoriasis, there are divergent opinions as to whether parapsoriasis is a precursor of mycosis fungoides. Keil (178b) stated that practically all cases of parapsoriasis en plaques represent an incipient stage of mycosis fungoides. However, L. McCarthy (224b) expressed the opposite view, since he believed the common forms of parapsoriasis remain as such and do not eventuate in mycosis fungoides or other lymphomas. Montgomery and Burkhart (245d) reviewed 52 cases of various types of parapsoriasis in

differ on the exposed or covered parts of the body There were psoriasiform lesions with thin silvery loosely attached scales on an erythematous base with little or no infiltration on the extremities and trunk which were not limited to the extensor surfaces and were from 2 to 8 cms in size On the forehead trunk and extremities there were 2 cm circular fungating lesions which had a keratotic surface On the shoulders sternocleidomastoid region back pelvis thighs knees and legs particularly on the left hip and right forearm were larger arciform circinate irregularly shaped infiltrated areas some of which were ulcerated exposing a purulent pink base These punched out ulcers were sharply marginated and from 4 to 8 mms deep Examination of the lungs revealed soft coarse rales over the upper one third anteriorly and posteriorly Examination of the abdomen disclosed deep tenderness about the umbilicus There were varicosities of the right scrotum and of both legs Gastrointestinal roentgenogram disclosed an Ulcer crater in the stomach and the colon was reported as Spastic markedly contracted Urine examination disclosed one to two red blood cells and six to ten white blood cells per high power magnification Treatment consisted of ACTH 25 mg four times a day for four days nitrogen mustard was given for four consecutive days one ampule in 500 cc saline This treatment produced nausea Two treatments with P 32 were given the first of four millicuries and the second of 4 29 millicuries The cutaneous lesions did not improve with this therapy Cortisone was administered for 14 days beginning with 50 mg a day and increased until 200 mg a day was given on the last day This therapy was believed to have been of definite benefit to the cutaneous lesions and was supplemented by ultraviolet irradiation to selected areas all of which improved

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TABLE X (continued)

	Parapsoriasis en Plaques	Mycosis Fungoides
Evolution of Eruption	Usually slow may be unchanged after many years duration	Usually appears and disappears in two to three years Tumor formation
Pruritus	Usually absent	Often present
Response to Therapy	Usually resistant Occasionally temporary improvement with calciferol No improvement with roentgenotherapy	May improve with roentgenotherapy No response to calciferol

TABLE XI

AMERICAN CLASSIFICATION OF PARAPSORIASIS

Guttate Type	
Chronic	Parapsoriasis en goutte (Brocq) Dermatitis psoriasiformis nodularis (Jadassohn) Pityriasis lichenoides chronica (Juliusberg)
Acute	Pityriasis lichenoides et varioliformis acuta (Mucha Habermann)
Parapsoriasis en Plaque	Erythrodermie pityriasique en plaque disseminées Xanthoerythrodermie perstans Parapsoriasis maculata
Retiform Type	Parapsoriasis lichenoides (Brocq) Parakeratosis variegata (Unna Pollitzer Santi) Lichen variegatus (Crocker) (This form is not recognized by some investigators)

After reviewing the literature on this subject Keil (178a b) concluded that practically all patients with parapsoriasis en plaques have an incipient stage of mycosis fungoides However on the basis of histological studies in a large series of cases L McCarthy (224b) believed that parapsoriasis guttata and parapsoriasis en plaques remain as such and do not eventuate in either mycosis fungoides or any other lymphomatous disease Both agreed however that there is a close relation

which the diagnosis was confirmed histologically Many of these patients had been studied for a number of years but there was no evidence of transition to mycosis fungoides or other lymphomatous diseases However, six additional cases were described in which the diagnosis was parapsoriasis en plaques clinically but histologic examination revealed mycosis fungoides and the disease terminated as such Ingram (164) reviewed parapsoriasis and suggested that pityriasis lichenoides is a self-limited disease which resolves spontaneously and does not give rise to sequelae He also believed that pityriasis lichenoides should be included in the group of parapsoriases whereas true parapsoriasis may develop into one of the many types of malignant reticuloses having a fatal outcome

The following table shows the essential differential diagnostic points between mycosis fungoides and parapsoriasis en plaques

TABLE X

DIFFERENTIAL DIAGNOSTIC POINTS BETWEEN PARAPSORIASIS AND MYCOSIS FUNGOIDES

	Parapsoriasis en Plaques	*Mycosis Fungoides*
Sites of Involvement	Usually involves legs (thighs) arms trunk rarely the head hands feet	May involve the head frequently the chest
Shape of Lesions	*Round or oval* usually along axis of extremities or parallel to ribs	Annular polycyclic tend to clear in center
Borders of Lesions	Ill defined	Sharply defined
Color of Lesions	Rose to yellowish pink	More erythematous
Surface of Lesions	Varnish like slightly scaling (thin scales)	Not scaling or covered with heavy crusted scales lichenified
Consistency *of* Lesions	*Not infiltrated*	Often infiltrated

mon type while group one may show a characteristic evolution into a reticular poikilodermic aspect An important histologic sign is the presence of small spaces containing one or more lymphocytes in the epidermis and sometimes a band formation which replaces the basal cell layer almost without interruption In Lapiere s experience one in four cases of parapsoriasis eventuated in mycosis fungoides sometimes very abruptly Mycosis fungoides lesions usually occurred outside the parapsoriatic plaques and were preceded by increased pruritus It was his opinion that all cases of parapsoriasis are potentially mycosis fungoides

The clinical diagnostic points between parapsoriasis en plaques and early mycosis fungoides were described in detail by L McCarthy (224b) He emphasized the lack of induration present in parapsoriasis and the tendency of the plaques to fade out into normal skin rather than to have the sharply defined margins usually present in mycosis fungoides However in the early stages of mycosis fungoides many of the lesions are eczematoid and sometimes transitory Although pruritus is usually mentioned as an early and prominent symptom of mycosis fungoides Montgomery and Burkhart (245d) found a number of patients who did not have this symptom for many years Since mycosis fungoides may remain in the early premycotic stage for many years without tumor formation ulceration or appreciable progression the duration of the disease is not a helpful diagnostic point Therefore in some cases it is difficult or even impossible to differentiate clinically between premycotic mycosis fungoides and parapsoriasis en plaques They described the histologic changes of early mycosis fungoides as demonstrating an infiltrate composed of a multiplicity of cell types with pyknosis and karyorrhexis of individual cells and clumping of cells Since a somewhat similar picture with clumping of endothelial cells is present in atopic eczema or generalized neurodermatitis they believed it difficult to distinguish between the two conditions This differentiation becomes even more difficult in early mycosis fungoides when eczematoid changes or early eczematoid

ship between so called parakeratosis variegata to poikiloderma and mycosis fungoides. There is also practically universal agreement that parapsoriasis guttata does not eventuate in mycosis fungoides or lymphoma. L. McCarthy (224b) emphasized that when a clinical diagnosis of parapsoriasis is found to be early mycosis fungoides on histological examination the clinical diagnosis is invariably in error since it is very rare for parapsoriasis en plaques to eventuate to mycosis fungoides. The patient described by Cornbleet and Schorr (67b) exemplifies this. In many cases described by Keil (178a, b) to illustrate this transition the diagnosis was based only on early clinical findings. However, Montgomery and Burkhart (245d) believed that some cases apparently begin as parapsoriasis en plaques and eventuate in mycosis fungoides. The patient described by Gougerot and Burnier (139d) had nonpruritic cutaneous lesions for 18 years and the histologic studies done by Elrascheff were consistent with a diagnosis of parapsoriasis en plaques and no evidence of mycosis fungoides was apparent. Poikiloderma like cutaneous changes occurred four years later and six years after the first histologic studies both the clinical and histologic picture were typical of mycosis fungoides.

Parapsoriasis en plaques was believed by Lapiere *et al* (197e) not to be a premycotic disease although they considered them to belong to the same group of diseases and to have the same unknown etiology. They were of the opinion that parapsoriasis is hypergeric and mycosis fungoides anergic and suggested that therapy should be directed against altering these factors in order to prevent the development of mycosis fungoides in cases of parapsoriasis en plaques or in curtailing symptoms in an established case. Lapiere (197c) divided parapsoriasis en plaques into three types with regard to the evolution and prognosis. These include cases having 1) clinical symptoms and histopathologic characteristics of mycosis fungoides 2) histologic mycosis fungoides and the clinical course of parapsoriasis 3) persistance of parapsoriasis both clinically and histologically. This third group is the most com

mon type while group one may show a characteristic evolution into a reticular poikilodermic aspect An important histologic sign is the presence of small spaces containing one or more lymphocytes in the epidermis and sometimes a band formation which replaces the basal cell layer almost without interruption In Lapiere s experience one in four cases of parapsoriasis eventuated in mycosis fungoides sometimes very abruptly Mycosis fungoides lesions usually occurred *outside* the parapsoriatic plaques and were preceded by increased pruritus It was his opinion that all cases of parapsoriasis are potentially mycosis fungoides

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in indurated lesion of the penis and regional lymphadenopathy appeared The condition became generalized by metastatic involvement of the abdominal and thoracic regions and proved to be lymphosarcoma which terminated fatally in one year Another patient described by Lane developed Hodgkins disease proved at autopsy five years later and another developed mycosis fungoides



78 Clinical features of poikiloderma like changes in a patient with mycosis fungoides (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

A 40 year old man described by Gougerot and Burnier (139d) had brownish red plaques on the trunk, face and extremities for 22 years The plaques were covered with delicate easily removable scales beneath which was a smooth glistening surface similar to that of parapsoriasis en plaques Four years later the changes had become intensified and the extremities were covered with a network of pigmentation atrophy and telangiectases typical of poikiloderma However five years later the patient had a fully developed mycosis fungoides A

plaques occur, since these plaques are often transitory, disappear spontaneously and frequently do not present the histopathologic picture of the disease Montgomery and Burkhart concluded that parapsoriasis en plaques should not be regarded as a "prelymphoblastomatous" disease Parakeratosis variegata and parapsoriasis en plaques rarely eventuate in mycosis fungoides or lymphomas Histologic studies frequently reveal clinical parapsoriasis to be a lymphomatous disease Parapsoriasis guttata does not eventuate in mycosis fungoides

A woman, described by Bluefarb and Ihrke (38c), developed cutaneous lesions of parapsoriasis five years before the nodules of mycosis fungoides appeared and, subsequently, carcinoma of the cervix All three diagnoses were made by histological examination

*3. **Poikiloderma Atrophicans Vasculare.*** Poikiloderma atrophicans vasculare is a symptom complex which may occur in association with many diseases, including any of the various lymphomas, and is not a clinical entity

The correct diagnosis of poikiloderma atrophicans vasculare is established by the presence of bright red cutaneous marking, telangiectasia, pigmentation, atrophy (especially in localized processes on the head and trunk) adherent scaling and simulation of roentgen ray dermatitis

In a comprehensive study of this subject, Oliver (259d) pointed out that when the disease is observed for a sufficiently long period of time it is usually identified as a phase of chronic inflammatory dermatitis He described a patient with circumscribed poikiloderma like lesions which later became infiltrated and the diagnosis of mycosis fungoides was established However, on the first presentation of this patient Senear (310b) and Finnerud (105b) both suggested the possibility of the premycotic stage of mycosis fungoides

Ormsby's patient described by J E Lane (196), was a 33 year old man who apparently had the condition since childhood Two hard tumors which were excised, had appeared on the back *two months previously Hemogram* revealed 10 per cent eosinophils and a slight leukocytosis He developed

dermatomyositis may develop as a result of damage caused by the same etiologic agent which produced the other disease and mycosis fungoides may also be due to noxae when occurring with poikiloderma Therefore O Leary believed it advisable to consider poikiloderma as a development resulting from the influence of various agents rather than as having a distinct etiologic factor

The following case is a typical example of mycosis fungoides with poikiloderma like changes

Case Report A 67 year old man first developed a patch of dermatitis in the right inguinal region one year previously Red patches gradually appeared on other areas until the trunk, arms and thighs were involved The eruption was markedly pruritic and consisted of irregularly shaped plaques from 2 cms in diameter to one involving half of the cutaneous surface of the thigh The lesions were sharply circumscribed with little or no infiltration only a few were slightly raised and some profusely covered with loosely attached fine scales A large erythematous atrophic pigmented telangiectacic area involved the right axilla and several similar lesions were present on other parts of the body There were no lesions on the scalp face mucosa hands or feet and there were a few small nontender epitrochlear lymph nodes

4 Congenital Ichthyosiform Erythroderma Congenital icthyosiform erythroderma as a possible precursor of mycosis fungoides was described by Beerman and Thomas (19) Their patient was a 54 year old Negress who developed acute chills fever and coma lasting 12 hours seven years previously which was followed by a red scaling dermatitis on the face This eruption became generalized with no remissions and was more marked during the winter season At 36 years of age the uterine cervix was amputated and irradiation therapy administered for carcinoma There w[illegible]
later

was m

and five years later At 51 years of age she had verrucoid hyperkeratotic patches on the extremities and an indurated

patient having poikiloderma atrophicans vasculare, mycosis fungoides, basal cell epithelioma and squamous cell epithelioma, was described by Leavell *et al* (203) Bloom (37) presented a patient with poikiloderma atrophicans vasculare with the histologic changes of mycosis fungoides Mycosis fungoides developing from poikiloderma which had been present for 11 years was reported by Gaté and Michel (124b) Ulcers and late tumors had been present for the last few months Patients having similar evolution of poikiloderma were described by Civatte (65a) and Gougerot and Blum (139b)

A 39 year old woman who had the characteristic Jacobi type of poikiloderma and the histologic features of no other disease for 14 years was described by Dostrovsky and Sagher (87) Numerous tumors then developed on the involved areas, producing a picture typical of mycosis fungoides of the tumor stage which was verified histologically Tumors continued to develop on all areas of the body and she died seven months after the onset of the tumors They also observed another patient whose initial cutaneous lesions appeared to be parapsoriasis en plaques, later poikiloderma, but following the development of tumors, histologic studies revealed mycosis fungoides Dostrovsky and Sagher believed too little emphasis is given to the fact that poikiloderma may be a symptom of chronic inflammatory dermatosis and in their case, should be considered the initial or premycotic stage of mycosis fungoides Poikiloderma, however, may be the terminal stage of numerous dermatoses They believed that poikiloderma may represent a particular reactional mechanism of the skin which may be stimulated by various agents which in this case, was mycosis fungoides

O'Leary (258b) was of the opinion that the cutaneous picture of poikiloderma atrophicans vasculare results from damage by various noxae to the cutaneous vascular structure and may involve deeper structures than the skin Poikiloderma has been reported in association with mycosis fungoides, disseminated lupus erythematosus dermatomyositis and idiopathic atrophy Poikiloderma, following disseminated lupus erythematosus or

the rectum extending to the perirectal lymph nodes was confirmed by an abdominoperineal resection. Three months later she had edema of the legs most marked at night and histologic examination of an enlarged inguinal lymph node revealed metastatic infiltration. She died of cardiac failure and the autopsy revealed bilateral pleural effusion, metastatic carcinoma of both lungs, liver and various lymph nodes.



80. Histological section of lesions (Ill. 79)

Since congenital ichthyosiform erythroderma is a rare condition it cannot, according to Beerman and Thomas (19), be a common premycotic lesion. However, if one concedes that congenital ichthyosiform erythroderma may be a premycotic phase of mycosis fungoides, there are many questions still unanswered as to the exact relationship of the two processes. 1) Will all patients with congenital ichthyosiform erythroderma eventually develop mycosis fungoides if followed long enough? 2) Are the two diseases separate entities but based on the same constitutional background? 3) Does the presence of



79 Mycosis fungoides with poikiloderma-like changes

ulcerative lesion near the mouth, associated with lymphadenopathy There were similar ulcerative tumor masses on the forehead and left thigh, and painful masses on the upper lip and chin Histologic examination of a lesion near the mouth revealed marked pseudoepitheliomatous hyperplasia and a multiplicity of cell types in the corium, while a forehead lesion showed the same picture as well as numerous eosinophils in the corium Seven months later she developed diarrhea and weight loss, and two months later a diagnosis of carcinoma of

VIII

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

THE DIAGNOSIS of mycosis fungoides particularly in the pre fungoid stage may sometimes be difficult However when a chronic ambiguous pruritic dermatitis which is rebellious to ordinary treatment assumes the form of psoriasis eczema urticaria or lichenoid prurigo the possibility of mycosis fungoides should be considered Other suggestive phenomena are intense pruritus without visible scratch marks the generalization of the eruption and resistance to therapy

In differentiating mycosis fungoides from parapsoriasis a slight fullness or rising of the skin at the edge is apparent in mycosis fungoides while the skin is thrown into folds with a slight depression or atrophy in parapsoriasis (see Table X)

A helpful diagnostic test was described by Lereboullet (206) He found that subcutaneous injection of 0 001 cc of epinephrine is followed by hypereosinophilia Injection of adrenalin will normally cause contraction of the spleen producing a sudden increase of erythrocytes However *in* mycosis fungoides there is a sudden increase of eosinophils

The diagnosis of mycosis fungoides is not difficult *in the* infiltrative or the tumor stage *when* histological examination will usually confirm the diagnosis The tumors must be differentiated from granulomas such as *syphilis tuberculosis* leprosy yaws bromoderma deep fungus infections melanosarcoma Kaposi's sarcoma metastatic *carcinoma dermatofibrosarcoma* leukemia and Hodgkin's disease

Leukemia cutis lymphosarcoma and Hodgkin's disease are the principal diseases to be differentiated in the *tumor stage*

congenital ichthyosiform erythroderma lead to increased susceptibility to mycosis fungoides? Because of the rarity of this condition, these questions cannot be answered as easily under present circumstances as they might be for the relationship between mycosis fungoides and poikilodermic states, and certain forms of parapsoriasis and other erythrodermas, according to Beerman and Thomas

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Hodgkin's disease first affects the lymph nodes and involves the skin secondarily, although there are numerous reports of autochthonous formation of Hodgkin's disease in the skin. Mycosis fungoides first affects the skin with secondary involvement of the lymph nodes. In the tumor stage of Hodgkin's disease the histologic picture shows the typical Sternberg-Reed giant cells, whereas in the comparable stage of mycosis fungoides the mycosic cell is present. Necrosis occurs in both conditions but a more fibrinoid caseation necrosis is present in Hodgkin's disease, whereas there is a liquefaction necrosis in mycosis fungoides. There is a pronounced tendency to sclerosis in Hodgkin's disease, a feature seldom present in mycosis fungoides. There are characteristic cells in mycosis fungoides, large monocytes (the so-called mycosic cells) which are most frequently present in the tumor rather than in the infiltrative stage. There are more fibroblasts and a greater tendency to fibrosis in Hodgkin's disease. However, definite diagnostic criteria cannot be derived from the study of a single feature but rather from the entire histopathological picture.

The characteristic features of leukemia cutis are the purpuric manifestations, involvement of the bone marrow and peripheral blood, the leonine facies (a common feature of leukemia and a rare one in mycosis fungoides). The histologic characteristics of leukemia cutis consist of dense cellular infiltrations without mitotic figures and the zone of normal connective tissue between the epidermis and the proliferating cellular infiltrations.

Lymphosarcoma is characterized by a greater uniformity of all types and a band of normal cutis present between the proliferating cells and the epidermis. Mitotic cells are present in lymphosarcoma.

To facilitate the proper diagnosis and to clarify some aspects of this complex situation, Beerman and Thomas (19) suggested the following: 1) Careful, detailed records of all clinical events. 2) repeated histologic studies at intervals of ALL dermatoses of obscure character or long duration or of unusual resistance to therapy. 3) prolonged follow-up observa-

tion even after apparent and unexpected "cure" or improvement, 4) careful roentgenologic studies (pulmonary, gastrointestinal, renal and bone), 5) repeated general medical and special examinations, 6) hematologic study by accepted methods, including repeated cytologic investigations of blood, bone marrow and lymph nodes These would include the oxidase test, special connective tissue stains and study of the bone marrow by the trephine method which preserves the form and relationship of the bone marrow cells, and, if possible, lymph node and skin impressions, and autopsy studies of the liver and spleen, 7) tissue culture, 8) the use of new investigative methods applicable to this problem from any field of medicine, and 9) central registry of a suitable center of all such obscure dermatological cases Correlation of the data in this center with related centers in other fields (i e, Tumor Registry)

IX

PROGNOSIS

THE DIVERGENCY of opinion regarding the duration of life in mycosis fungoides appears to result from grouping of the three types which are described as mycosis fungoides. The "d'emblee" type may be of extremely short duration, often only a matter of weeks or months. The erythroderma type also appears to run a fairly rapid course. However, classical *mycosis fungoides is frequently of much longer duration*. The premycotic stage may be present for many months or years while the infiltrative stage tends to run a more rapid course. Adequate treatment, including roentgenotherapy, may result in prolonged, useful life, especially for patients having only cutaneous involvement of the classical type.

Binder (33) stated that he did not believe the morbidity of mycosis fungoides to be increasing. In the past this has shown fluctuations and, in his opinion, earlier diagnosis and the present greater life expectancy probably account for the increase in cases today. Even with present day therapy, however, Sequeira (311b) believed it impossible to do more than give relief of symptoms and prolong life. The slow, painful course of the disease may be rendered less severe in many cases and the intense agonizing pruritus may be somewhat alleviated. Pautrier (268e) stated that a patient, seemingly in good health may develop large generalized tumors and still remain "in the most amazing state of well being." He believed that one should suspect mycosis fungoides when this situation occurs. He described the unpleasant features of *mycosis fungoides* as the long "horrible" course and bodily disfigurement, although the preservation of bodily function continues.

Any *of the various lymphomatous diseases may* terminate

fatally, according to Montgomery (245c) who lists the following from a standpoint of longevity when involvement is confined to the skin Mycosis fungoides, Hodgkin's disease, chronic leukemia and lymphosarcoma and acute leukemia Although spontaneous involution without therapy, particularly in cases of primary cutaneous exfoliative dermatitis of various etiology may occur, typical cutaneous or systemic lymphomatous manifestations may occur years later Fraser (114b) commented on the spontaneous resolution of tumors which is characteristic of mycosis fungoides but has also been observed in other conditions Spontaneous resolution of individual lesions has also been noted in Kaposi's sarcoma and in lymphosarcoma particularly the reticulum cell type Ewing (100) referred to a patient having reticulum cell lymphosarcoma of the tonsil which underwent complete resolution following removal of tissue for histologic study but later appeared in another area This same spontaneous resolution occurred in a patient observed by Trimble (339b) following removal of tissue from a primary lymphosarcoma of the cheek A few weeks later a tumor developed in the eyeball which had the same histologic structure as the cheek lesion

A patient who had typical clinical and histologic mycosis fungoides described by Helmke (151) was well 16 years after the lesions had cleared completely following therapy One of Pautrier's (268e) patients survived for 23 years after roentgenotherapy He described another patient who presented diagnostic difficulty in that the only clinically demonstrable lesions for a period of 30 months were a "weeping eczema"

Jordan and Areschewa (174) presented a statistical study of 136 cases of mycosis fungoides, from the literature and their own cases This study included all cases in which there was sufficient data to warrant inclusion Of these cases 68 were followed from one to five years 38 from six to 10 years, eight from 11 to 15 years five from 16 to 20 years one for 24 years and one for 30 years In 15 cases the time of observation was not stated Only 38 patients were followed to a fatal termina

tion Of these, death came as a result of cachexia in 10, probably from roentgen ray damage in 10, metastases to the internal organs in four, complications occurring in the lungs, heart and brain or endocrine glands in five, of intercurrent disease in one and of unstated causes in eight

MacKee (228a) believed the longevity of these patients to be of interest Most patients having mycosis fungoides die within five to ten years, some in two or three years, although reports of 18 or 20 year survivals appear in the British literature He summarized the history of a patient who had just died of pneumonia This man was first examined 17 years previously at which time he was over 70 years of age He presented a generalized cutaneous eruption consisting of infiltrated pruritic plaques He had been treated for similar eruptions during the preceding 10 years However, these recurrent eruptions had been exceptionally responsive to roentgenotherapy and the generalized eruption, 17 years before, was the last attack of this type Every year or two thereafter he developed two or three small tumors which disappeared with a single dose of three quarter skin unit, unfiltered roentgen rays However, during the *last few years the tumors* had required two or three more erythema doses of filtered radiation This patient had remained alive and comfortable for about 25 years and it was a comparatively benign case although MacKee believed that he would not have lived for long had it not been for the roentgenotherapy he received These tumors had been present for at least 15 years although patients usually die within a few weeks after the onset of the tumor stage according to MacKee

Netherton (251) also stated that the tumor stage is of short duration although there have been reports of this stage continuing for 18 years He described a woman who had scaly pruritic lesions for eight years before the development of infiltrative lesions Heite and Socha (150) stated that more than 50 per cent of patients having mycosis *fungoides survive* for five years and 20 per cent live more than ten years

In reviewing the duration of life in mycosis fungoides

Sequeira (311b) found the longest duration 35 years, was reported by Stopford Taylor (323) He found several reports of 20, or more, years duration and "we all must have seen patients who had dragged on in miserable existence for five or 12 years" Among the cases which came to autopsy, he found that pulmonary embolism was given as the cause of sudden death in only one case White and Burns (360) reported a patient who died of septicemia which they believed was due to roentgenotherapy

Thomson (332b) believed the prognosis of mycosis fungoides to be "most gloomy," and although some patients might survive for a very long time, he was of the opinion that the average duration was no more than 10 years after the appearance of the initial symptoms He did not believe that visceral infiltration had any effect on the prognosis and, since the disease might continue for many years with comparatively long remission periods the value of therapy was difficult to access

X

TREATMENT

More varied therapy has undoubtedly been employed in mycosis fungoides than in any other lymphomatous disease. However, there is still no convincing evidence that any of the therapeutic agents to be discussed have even temporarily restored the malignant tissues in any patient to a completely normal architecture and cell distribution according to Block *et al* (35d).

The therapy of mycosis fungoides, like that of other lymphomatous diseases, may be divided into internal and external therapy. External therapy is usually of a physical nature whereas internal treatment usually consists of chemotherapy.

TABLE XII

Therapeutic Agents

External Therapy	*Internal Therapy*
Roentgen Rays	Drugs
Radium	Arsenic
Grenz Rays	Nitrogen Mustards
Thorium X	Triethylene Melamine (TEM)
Ultraviolet Light	Urethane
Topical Medications	Colchicine
	Antimony Derivatives
	Chaulmoogra Oil
	Testosterone
	Paraaminobenzoic Acid
	Teropterin
	Corticotropin (ACTH) and Steroids
	Other
	Radioactive Isotopes
	Hyperpyrexia
	Symptomatic Blood Transfusions

Although there are numerous therapeutic agents, all have several common characteristics which probably account for their efficacy. Block and Jacobson (35a) stated that each of these agents is primarily destructive to small lymphocytes and, to a lesser extent, to erythroblasts, myelocytes, granulocytes and megakaryocytes, but not to reticulum cells, the basic cell in all hematopoiesis. Those agents which affect the whole body diffusely, such as nitrogen mustards, radioisotopes and total body irradiation, have been clearly shown to inhibit antibody formation as well as cellular inflammatory responses, according to Jacobson *et al.* (166).

Therefore, it is apparent that the present form of therapy for mycosis fungoides cannot be curative, since present treatment is not directed at the basic stem cell, the reticulum cell. Therapy can do no more than control the symptoms of the disease and, frequently, prolong life. Any attempt to "burn" out the disease is doomed to failure for theoretical and practical reasons and will result in complications more distressing than the original disease.

Localized roentgen rays, nitrogen mustard or urethane and antimony compounds appear to be the more frequently employed forms of therapy at the present time. Combinations of therapy may also be employed. Patients having a few large, persistent ulcers or fungating lesions remaining after nitrogen mustard or urethane therapy may be given localized roentgenotherapy.

A. External Therapy

Roentgen Rays. Prior to 1902 the treatment of mycosis fungoides consisted of the administration of arsenic and mercury, but both drugs were found to have little favorable influence on the disease. Scholtz (305), in 1902, was the first to use roentgenotherapy for mycosis fungoides while Belot (22) in France, W. A. Jamieson (171) in England and Sherwell (315) in the United States were the first to use roentgenotherapy for this disease in their respective countries. Previous therapy and to a greater extent, present therapy, fundamentally

involves local or systemic roentgenotherapy plus various local and systemic palliative measures for the relief of pruritus

Roentgen rays are undoubtedly capable of modifying the course of mycosis fungoides Although the cutaneous lesions may undergo involution following local or systemic roentgeno therapy, they eventually recur months or years later Inasmuch as this therapy is merely palliative, the dosage should usually be moderate

There appear to be only two authentic case reports of permanent "cure" following roentgenotherapy Cannon (58b) described a 35 year old woman who had about 300 cutaneous nodules and tumors, a few of 'grapefruit size All the lesions disappeared following roentgenotherapy and weekly injections of neoarsphenamine and had not recurred 30 years later A woman who had no recurrence of the lesions 22 years following prolonged roentgenotherapy was reported by Lommen (216)

Although the cutaneous lesions of mycosis fungoides may often respond spectacularly to roentgenotherapy, these results are not permanent since the involved areas are apt to be more radiosensitive than the surrounding skin Lesions which may at first be extremely sensitive to irradiation may finally cease to respond to large doses and, therefore, large doses are not required for treatment The results are usually excellent with fractional doses Treatment consisting of 75 r weekly is generally advocated, particularly at the beginning of therapy, to prevent possible toxemia In the event generalized or nearly generalized irradiation is required the body surface is divided into three or six areas depending on the distribution of the eruption Each body area is treated once weekly although no more than one or two areas are treated on any one day The initial dose is 38 r unfiltered radiation but after two or three weeks of treatment this dose may be increased to 75 r if necessary If the lesions show no response to roentgeno therapy it should be discontinued and other forms of therapy instituted It is usually unnecessary to use filtered radiation excepting for the treatment of tumors since the lesions of mycosis fungoides yield readily to roentgen rays of any quality

according to MacKee and Cipollaro (228c) They stated that the tumors usually show complete regression following a single exposure of filtered low voltage roentgen rays (500 to 550 r 140 kv 3 to 4 mm aluminum filter 30 cm distance) Thin superficial cutaneous plaques ulcerated or nonulcerated may yield completely to as little as 300 r low voltage roentgen rays either unfiltered or filtered through 1 mm of aluminum The lymph nodes and deeper lesions such as those involving the
doses (300

to be fol lowed in roentgenotherapy of mycosis fungoides "In the stages of dermatitis and superficial infiltration the lesions will respond to therapy of low voltage unfiltered rays The formula advised is as follows 60 to 100 kv 3 to 5 ma 15 to 20 cm focal skin distance and inherent filtration of the tube The approximate half value layer for this formula is 1 to 1 5 mms of aluminum The dosage (free air exposure measured at the surface of the skin) varies from 75 to 100 r per area weekly The individual lesions respond to a total dose of 600 to 800 r The areas treated are screened off to include a border of normal skin of approximately 0 5 to 2 cms It must be remembered that the amount of back scatter varies with the half value layer and attains a maximum at a half value layer of *about 0 4 to 0 6 mm of copper* This value is usually obtained with a kilovoltage of 150 and a filtration equivalent to 2 to 4 mms of aluminum or 0 25 mm of copper When the voltage is increased above this value the back scatter is decreased This would of course lower the skin dose for a given air dose Areas such as the thyroid testes and hairy regions should be properly shielded

Generalized Roentgenotherapy Sommerville (320a) who described the "shower bath" type of roentgenotherapy reported a 50 year old man who had a scaly cutaneous eruption on the lower extremities associated with pruritus for one year The eruption then became generalized to involve the entire body with a moist scaly erythematous dermatitis most marked on

the legs The legs and scrotal region were markedly edematous Portions of the skin had a bluish hue, and there were a number of tumor masses on the trunk, some of which were beginning to fungate The diagnosis of mycosis fungoides was confirmed histologically The body was divided into two large fields, roughly representing circles of 80 cms in diameter Therapy consisted of a kilovoltage of 200, h v l 1 9 distance of 200 cms, 10 r per day at the rate of 2 r per minute to each area, until he had received a total of approximately 900 r The general reaction was profound, but nine months after cessation of therapy both the general health and the skin condition were good In a later discussion, Sommerville (320b) reported this patient to be in good health 13 years later, and he had survived two attacks of exfoliative dermatitis Because of the extremely severe reaction, he believed this type of therapy should be undertaken with great care since the patient must be 'hit" hard enough to produce a very sharp blood reaction However, the results obtained from this form of therapy are not notably better than those obtained with superficial roentgen rays and the danger of the marked anemia which follows therapy in the Heublein unit is not present

The toxic reactions which may follow intensive roentgenotherapy vary from toxic cutaneous eruptions resembling erythema multiforme to agranulocytosis and death When treating generalized dermatoses, particularly radiosensitive diseases such as mycosis fungoides, a febrile reaction may develop together with a toxic dermatitis and the original eruption may become more manifest These phenomena may result from the rapid absorption of toxic material from the involuting lesions The patient reported by Duverne *et al* (94) developed a fatal agranulocytosis following roentgenotherapy for a premycotic erythema

Cathode rays which have the same biologic effect as x rays have limited penetration into the skin depending upon the voltage used, and electron energy can be localized to the superficial layer of the skin The entire body may be irradiated at one sitting without evidence of bone marrow depression or radiation sickness in any case At 2 5 million electron volts the

peak ionizing dose lies at 3 to 4 mm. beneath the affected skin where it effectively localizes and exerts its biologic action in the pathologic infiltrate seen in this disease

Radium Radium is of limited value in the treatment of mycosis fungoides and is used in the mouth auditory canal and other areas inaccessible to roentgen rays or in the treatment of circumscribed lesions in any area

Grenz Rays The safety factor of Grenz rays makes this an excellent modality for the treatment of mycosis fungoides (Bluefarb 38a) This therapy may be repeated with safety when the disease becomes active following remission whereas the amount of roentgen irradiation which may be administered with safety is limited Kalz (175) reported a 63 year old man who had markedly pruritic generalized infiltrated cutaneous lesions of mycosis fungoides Following Grenz ray therapy, the symptoms were completely relieved for many months He believed Grenz rays give excellent results in cases not having internal lesions or other complications of mycosis fungoides Despite the fact that this therapy is not curative it may lengthen the patient's life and there may be remissions without symptoms for many years Cernohorsky (59) used Grenz ray therapy in four cases of mycosis fungoides and found there was a favorable influence on all stages of the disease The sensitivity of the different clinical manifestations varied greatly The premycotic eruptions improved after doses of 800 to 1000 r with either total or fractional radiation and recovery *took* place in four to seven weeks The most rapid improvement was noted in the infiltrative stage which reacted to doses of 600 to 1000 r administered in one treatment Fractional radiation could be used equally well *but would require* a higher total dosage Recovery *required* three to six weeks The *tumor* stage manifestations reacted only to fractional therapy in doses of 300 to 800 r and a total dose of 4000 r was *necessary to obtain good results* while recovery took place in four to ten weeks He believed that successful treatment of the superficial layers of the skin enables the rays to penetrate to deeper portions of the tumors Relapses could not be predicted whether roentgen rays or Grenz ray therapy were used

Thorium X. Thorium X therapy was advocated by Russel (299) who stated "I believe that the local application of thorium X is the treatment of choice until tumors develop; then x-rays are necessary. Thorium X keeps the patients relatively comfortable and can be applied with ease and safety to extensive and patchy lesions without the risks associated with x-ray exposure over a wide area."

A patient who had received little benefit from roentgenotherapy was described by Green (141). Thorium X was then used in doses of 2,000 units in isopropyl alcohol painted on a small affected area of skin weekly for six applications. The erythema appeared to clear following the first application while the pruritus was completely relieved and continued in abeyance even after some relapse in the erythema. After many weeks without treatment the scaly erythema and pruritus recurred. Intravenous thorium X, 100 units in saline, was then given weekly, for 12 weeks, with some relief of the irritation and some of the erythema diminished. Although the differential blood counts were normal before, during and after treatment, Green was reluctant to continue this therapy. Thorium X, 2,000 units in isopropyl alcohol, was then resumed at weekly intervals for 12 weeks, applied to the entire left half of the back and on two square patches on the front of the trunk. The erythema and irritation again disappeared and the skin appeared normal. Four weeks later the two squares on the front of the trunk were not erythematous and the pruritus was completely relieved. There was slight erythema involving the side of the back to which thorium X had been applied, but there was no evidence of irritation. Green's second patient was treated with intravenous injections of thorium X, 100 units in saline weekly for 12 weeks. The irritation subsided considerably for the first few days following each injection, but the dermatitis and tumors were not benefitted. The blood studies were normal before and after each treatment. However, this therapy was not continued and thorium X, 2,000 units in isopropyl alcohol, was then painted on controlled areas of the body once weekly for 12 weeks. The erythema and exfoliation

diminished considerably on treated areas and the skin appeared more normal Feeny (103) believed that prior to this time thorium X was not used parenterally in dermatology, although it had been available since 1912 Radioactive thorium X injections were used extensively in France during the 1920s but the results were poor and bone necrosis as well as radiodermatitis were described Therefore Feeny believed that thorium X should be used only for topical therapy

Ultraviolet Light Ultraviolet light is primarily beneficial as an anti pruritic although definite clearing of the cutaneous lesions following this form of therapy was noted by Bluefarb and Ihrke (38c) Inasmuch as drugs employed in the present day treatment of mycosis fungoides have no effect on the basic stem cell the reticulum cell it would appear that superficial roentgen rays and ultraviolet light would be the treatment of choice for this disease because of the minimal risk to the patient

The three lymphomatous diseases having associated pruritus are Hodgkin s disease the exfoliative form of chronic lymphocytic leukemia and the premycotic stage of mycosis fungoides In all three there appears to be some relief of the pruritus following generalized ultraviolet light therapy Ultraviolet rays like roentgen rays appear to elevate the sensory threshold of the intraepithelial nerve endings

Topical Therapy With the exception of thorium X the only value of topical therapy in mycosis fungoides is for control of pruritus Antipruritic lotions and ointments are of some value

Phenolated Calamine Lotion N F IX

Liquefied Phenol	1 0
Calamine Lotion to make	100 0

Liniment N F IX

Calamine	8 0
Zinc Oxide	8 0
Olive Oil	50.0
Calcium Hydroxide Solution to make	100 0

Generalized tar baths, such as the proprietary preparations of Ar-Ex, Almay or Zetar (R) may be used Hydrocortisone ointment is often effective for the treatment of pruritus

The use of an ointment containing 1 per cent podophyllin for the relief of discomfort was described by Craig (70) The cutaneous lesions disappeared following application of this ointment and although they recurred a month or two later, re application again relieved the condition

The ulcerated tumors should be cleansed dressed aseptically and a soothing ointment, such as unguentum ichthammolis N F IX, applied to the lesions Darier (74) stated that the cutaneous tumors and infiltrations would occasionally absorb following the topical application of pyrogallol However, repeated urine examinations for albumin are required with this type of therapy

B Systemic Therapy

Arsenic. Arsenic was one of the first drugs to be used for the treatment of mycosis fungoides and continues to be a useful therapeutic agent However arsenotherapy offers only temporary benefit and the toxic reactions must be constantly considered It may be administered orally, intramuscularly or intravenously The oral preparations most frequently used are asiatic pills and Fowler's solution

Arsenic Trioxide (Asiatic Pills)

Arsenic Trioxide	0 1
Piper Nigri	5 0
Glycerine	3 0
Water	1 0

Potassium Arsenite Solution N F IX (Fowler s Solution)

Arsenic Trioxide	10 0 gm
Potassium Bicarbonate	7 6 gm
Alcohol	30 0
Distilled Water to make	100 0

Directions One drop in water or milk after meals three times daily Increase by one drop a day until 12 drops are taken daily

For Children

Fowler's Solution	5 0
Peppermint Water to make	15 0

Directions 1-3 6 drops daily depending on age

2 Per Cent Solution Sodium Arsenate (For Subcutaneous Injection)

Sodium Arsenate	2 0
Phenol	1 0
Sterile Distilled Water, to make	100 0

(In sterile fashion in rubber dam stoppered vial)

Directions One half cc daily or every other day, subcutaneously

The toxic reactions to arsenic include dryness of the throat, insomnia, edema of the eyelids, neuritis, diarrhea, hyperkeratoses of the palms and soles cutaneous hyperpigmentation and malignant cutaneous lesions

Neoarsphenamine and mapharsen are the most common forms of arsenic used for intravenous injection Cannon (58b) stated that his only patient having the tumor stage of mycosis fungoides who had remained well had received

leukemias and neoplastic diseases, according to Gilman and Philips (129) and Rhoads (291) This group of chemicals appears to affect the nuclear structure of the cell and resembles most closely the action of short wave radiation, rather than that of any other known chemical reaction Karnofsky (177) stated that a rapid and marked therapeutic effect is sometimes obtained which has continued for three, five or more, months

Henstell and Tober (153a) were the first to record the result of nitrogen mustard therapy for mycosis fungoides They treated a 67 year old woman with nitrogen mustard (methyl bis (2 chloroethyl) amine hydrochloride), dissolved in 5 cc distilled water injected into the tubing of an infusion of isotonic solution of sodium chloride, administered intravenously The same dose was repeated on two successive days They observed a prompt response to this therapy and the cutaneous

papules, infiltrations and pruritus began to diminish the fourth day following treatment. Nine days later the histologic report stated: "The intense infiltrate of earlier sections is gone." In a later report, Henstell *et al.* (153b) reported the results of nitrogen mustard therapy in six cases of mycosis fungoides. There was a marked immediate response to therapy in all cases, regardless of the type of mycotic cutaneous lesions present or the stage of the disease. All of these patients had been found to be radioresistant. In four cases (1,2,3,4) the disease had been present from eight to 30 years and had responded favorably to roentgenotherapy for an appreciable time but they had been radioresistant for several years. In two cases (5 and 6), the disease had been present for 30 and 15 months, respectively. Cases 1,2 and 3 had excellent response to therapy, the lesions cleared almost completely and the pruritus was greatly relieved. One patient (case 4), who had the disease for 30 years, showed only partial improvement. Cases 5 and 6 were considered to be clinical failures since there was a prompt response to this drug but each course was followed by relapse within several weeks, and the duration of improvement became increasingly shorter.

Kierland *et al.* (182) treated six patients having mycosis fungoides with nitrogen mustard. Three of these patients were given two courses of the drug. One patient, who had not received previous roentgenotherapy, died two weeks after nitrogen mustard therapy of a febrile disease which was not explained at autopsy. However, the infiltrated cutaneous plaques showed regression one week after treatment. Another patient, who was pregnant, had received roentgenotherapy to all cutaneous areas with the exception of the lower back and abdomen. All the irradiated areas improved and one month after roentgenotherapy a normal infant was delivered. Two weeks later, a course of nitrogen mustard therapy was administered, and within two weeks the pruritus improved and one week later, the tumors had regressed in size and degree of infiltration in the areas which had not been irradiated. Although her condition was improved two and one-half months later, new

tumors and recurrences of the nodules were apparent in some areas and a second course of nitrogen mustard was given Four patients in this group had received repeated courses of roentgenotherapy over a period of one to six years and had become resistant to radiation One patient showed a striking response to nitrogen mustard therapy She rapidly gained in strength and weight and the pain and pruritus almost disappeared The cutaneous infiltration and erythema rapidly subsided and she was discharged after continuous hospitalization for 10 months Six weeks later her general condition was still improving but the paroxysmal pruritus had recurred and she was given a second course of nitrogen mustard therapy The general condition and the cutaneous lesions responded to therapy in the other three cases One patient had relief of pruritus following the second course However the cutaneous lesions were disappearing and no new lesions had appeared two months after the second course of treatment The relief of pruritus was marked in two other cases one to two and one half months after treatment the original cutaneous lesions continued to improve and new lesions had not appeared The reactions to nitrogen mustard therapy were essentially of the gastrointestinal type according to Kierland *et al* All patients experienced nausea after the first injection and four had vomiting within three hours after the first injection Other reactions were disturbance of the formed elements of the blood such as leukopenia granulocytopenia and thrombocytopenia

A 79 year old man reported by Philpott *et al* (272) showed marked improvement with nitrogen mustard therapy as evidenced by involution of the cutaneous tumors and infiltrated plaques and diminution of pruritus However pancytopenia developed and despite transfusions of whole blood he died several weeks later Two patients who had advanced mycosis fungoides reported by Osborne *et al* (262) showed a temporary response to nitrogen mustard therapy The first patient a 54 year old woman developed new cutaneous nodules "some time" after treatment Fissured lesions appeared and she was unable to have further nitrogen mustard therapy The second

patient a 62 year old man had a recurrence one month after treatment and failed to improve with roentgenotherapy He died seven months after nitrogen mustard therapy Osborne *et al* concluded that the value of nitrogen mustard therapy for mycosis fungoides is principally limited to patients having far advanced stages of the disease probably with internal lesions who cannot be adequately treated with roentgenotherapy or those who have become radioresistant It is obvious they stated that further radiation therapy following nitrogen mustard therapy is essential and since there is an immediate dramatic relief of pruritus this factor had a great psychological effect on the patient

Goldberg and Mason (134) treated three patients having mycosis fungoides with nitrogen mustard and concluded that although not curative this therapy offered a symptomatic palliative method of treatment There was usually an immediate response to the first course of treatment with a demonstrable effect on the cutaneous tumors and plaques and the pruritus showed immediate improvement which lasted for a longer period than any visible cutaneous changes Although successive courses of treatment were found to be of value the temporary improvement of the cutaneous tumors and infiltrations appeared to diminish with subsequent nitrogen mustard therapy Repeated treatment was not found to produce severe blood dyscrasias or greater changes in the blood elements than those which occurred during the initial course of treatment Nitrogen mustard therapy did not appear to affect the microscopic infiltration in the cutis in these cases as substantiated histologically before during and after therapy They concluded that nitrogen mustard therapy has a more dramatic effect on mycosis fungoides than roentgenotherapy but offers no better prognosis

Detailed microscopic observations before during and following nitrogen mustard therapy were described by Block and Murphy (35c) They stated that the effect of nitrogen mustards on tissues is similar to that of ionizing radiations In the normal animal given median lethal doses of nitrogen mustard

the successive changes are as follows First there are cessation of mitoses and degeneration of susceptible cells (small lymphocytes myelocytes erythroblasts and megakaryocytes) The major part of the degeneration of susceptible cells occurs only in the hematopoietic tissues within 18 hours after injection not in the peripheral blood The outstretched fixed cells (fibro blasts macrophages and reticular cells) as well as plasmacytes are extremely resistant to the destructive action of the mus tards The second phase is phagocytosis of debris The third or atrophic phase lasts several days and corresponds to a period of aplasia of the susceptible cells and reduction of the number of mitoses Regeneration ensues as a result of hetero plastic formation of the susceptible free cells from the reticular cells and homoplastically by mitotic proliferation of the few residual susceptible cells There is no evidence to support the thesis that the nitrogen mustards exert their effect primarily on immature or rapidly dividing cells

These results with regard to the decrease in the infiltrate were in general confirmed by Henstell *et al* (153b) How ever there was little evidence of marked effect on *mycosis* cells in Block and Murphy s (35c) series except for the cessa tion of mitosis

Five patients having mycosis fungoides were treated with nitrogen mustard by Pillsbury and Urbach (273) They found that only 6 mg of nitrogen mustard given every day or every other day with intervals of "rest" were required Hammer berg and Bastrup Madsen (146) *reported* a 57 year old man who had extensive pruritic eczema and numerous tumorous infiltrates which revealed many reticuloendothelial cells with numerous mitotic figures on histological examination The lesions had been found to be *radioresistant* Three series of *nitrogen* mustard therapy resulted in a nearly complete dis appearance of the severe pruritus However *each remission* lasted for only one to two months

Burman (32) treated four patients with intraarterial injec tions of nitrogen *mustard* The fluorescein was injected first to determine the vascularity of the neoplastic tissue whenever

possible The nitrogen mustard was dissolved in saline solution in a concentration of 1 mg per cc, and injected at the rate of 10 mg per minute in doses of 5 to 80 mg of 0 1 to 1 mg per kilograms of body weight

Friedman and Stritzler (115) administered both anti reticular cytotoxic serum and nitrogen mustard to a patient having the ulcerative stage of mycosis fungoides There was no clinical improvement or histologic change following either type of therapy Evans *et al* (99) described a patient having mycosis fungoides "d emblee" who had marked regression of the cutaneous lesions and the superficial lymph nodes following nitrogen mustard therapy

The results of nitrogen mustard therapy in mycosis fungoides have also been reported by Owen (263), Desaive *et al* (83), Foldvari and Nekam (109) Felischhacker and Klug (108) Schaefer and Lehner (303) and Schulze and Brauner (308)

Triethylene Melamine Triethylene melamine, administered in 5 mg tablets for oral ingestion, has an action similar to nitrogen mustard, according to Hughes (161) He reported the results of this therapy in two cases of mycosis fungoides The first patient who had extensive, markedly pruritic confluent exfoliating cutaneous lesions, did not improve with this therapy and died two months later The second patient who had generalized discrete cutaneous involvement, had relief of pruritus and regression of the lesions for four months following treatment

Triethylene melamine tablets are taken orally, before breakfast, and the recommended dose is 10 mg for the first week Five to ten mgms may be given weekly for the next three or four weeks in the event that further therapy is required and the hemogram is normal The delayed reactions to this drug may be nausea and vomiting occurring six or more hours after ingestion which may persist for one or two days The hematological reactions consist of varying degrees of bone marrow depression

Urethane Urethane has been used for the treatment of mycosis fungoides since Paterson *et al* (267) employed this

therapy for leukemia Kennedy *et al* (180) administered this therapy to nine patients having mycosis fungoides They used a 20 per cent solution of urethane orally in syrup of raspberry Four grams daily were given routinely but the dose varied from 0 5 to 5 gms Among these nine patients who had various stages of mycosis fungoides four showed definite improvement with relief of pruritus regression of tumors and epithelization of ulcers Histologic studies revealed an obvious decrease in the density of the infiltrate The initial remissions varied from three to 19 months They stated that readministration of urethane may also be effective although repeated courses or persistent use of this drug causes increasing refractions of the disease such as occur following radiation or nitrogen mustard therapy The reactions from urethane may consist of anorexia nausea vomiting diarrhea drowsiness and leukopenia

Two patients described by Shaffer (314) showed marked improvement following urethane therapy The first patient received a total of 550 gms without any apparent toxic reaction Leinbrock (205) observed one patient for 23 months following the administration of 147 gms of urethane There was temporary involution of the tumors and infiltrate but persistent severe pruritus was followed by relapse secondary infection and death The normal cells of the spleen liver and lymph nodes were found at autopsy to be replaced by fibrous tissue The serum albumin was decreased but alpha and beta globulins were increased during urethane therapy The total protein and electrophoretic serum albumin changes paralleled the severe clinical course of the disease Leidel (204) reported a 50 year old woman who responded favorably to a total dose of 210 gms of urethane However leukopenia developed and the drug was discontinued She died following an exacerbation of the tumor formation The second patient was a 52 year old man who improved with urethane therapy His general condition improved considerably and the infiltrated cutaneous lesions and pruritus disappeared However the symptoms *recurred* later while urethane was still being administered

Three of the four patients treated by Musso (249) showed

temporary improvement while receiving urethane therapy The involution of the cutaneous lesions paralleled the development of leukopenia in one case The patient reported by Rehak (288) responded well to initial treatment with urethane but became refractory to the drug and further nitrogen mustard therapy proved to be ineffective Korting (189) described a 50 year old man who had received 74 gms of urethane during a period of seven weeks He then developed bilateral gynecomastia, presumably due to increased estrogenic substances which the damaged liver was unable to destroy, and increased urobilinogen excretion The gynecomastia slowly decreased after cessation of urethane therapy

Colchicine. The antimitotic action of colchicine has long been recognized but due to its high degree of toxicity and the lack of standardized preparations, its use has, heretofore, not been successful for the treatment of malignant tumors Recent studies, however, have led to the isolation from Colchicum autumnale of cytostatic para alkaloids which have an action similar to that of colchicine and which can safely be given internally One of these, designated substance F (12 669"–colcemid), which was found to have greater antimitotic action and less toxicity than colchicine was used by Midana and Ormeo (238) in treating three patients having mycosis fungoides and, for comparison, two having epitheliomas Complete remission of the clinical symptoms and a return of the histologic picture to normal were noted in the cases of mycosis fungoides but there was no improvement in those having epitheliomas The method of treatment was the same in all five cases and the drug was reported to have been well tolerated The initial dosage was one or two mgms daily which was increased to three mgms a day Two patients were treated with intravenous injections and the other three by oral administration The total dosages varied from 40 to 90 mg Investigators at the University of Vienna used preparation 12 669" in treating patients having granulocytic leukemia, sarcoma and carcinoma and concluded that its effect on connective tissue neoplasms differs from its effect on epithelial

tumors They reported clinical cures in patients having leukemia but those having epithelial tumors were not benefitted Since mycosis fungoides like leukemia belongs with the reticuloendothelial system diseases the results reported by Midana and Ormeo are in substantial agreement with those obtained at Zurich They stated that their report is intended merely to establish priority and to show the excellent results of therapy with this new preparation in cases of mycosis fungoides although a longer follow up period and further trial will be needed before its clinical value can be definitely determined

Antimony Compounds Garb (122b) who had extensive experience in treating mycosis fungoides with antimonial compounds stated that of the three antimony preparations he considered antimony potassium tartrate first stibophen second and stibanose (the diethylaminoethanol salt of sodium antimony gluconate) last in effectiveness He advocated 20 intravenous injections of a one per cent solution of antimony potassium tartrate three times weekly and treatment continued with stibophen or stibanose until all lesions were healed and weekly injections of stibophen or stibanose for six months Patients who responded to antimonials manifest pronounced improvement within three to six weeks but if there is no notable improvement within this period antimonials will probably be of little benefit The untoward reactions are described as arthritic pain usually affecting the shoulders cutaneous eruptions tachycardia bradycardia and other myocardial changes These changes are usually reversible within six weeks after discontinuance of treatment He suggested that a hemogram electrocardiogram and a liver function test should be done monthly in order to avoid serious complications In a later report Garb and Sims (122c) reported 11 cases treated with antimonials Of these four responded to treatment while seven were not improved

Ethylstibamine (Neostibosan) another antimony compound was used by Berkovsky (28) in treating a 56 year old man He was given intravenous injections weekly and some of the cutaneous lesions began involution and the pruritus diminished

temporary improvement while receiving urethane therapy. The involution of the cutaneous lesions paralleled the development of leukopenia in one case. The patient reported by Rehak (288) responded well to initial treatment with urethane but became refractory to the drug and further nitrogen mustard therapy proved to be ineffective. Korting (189) described a 50 year old man who had received 74 gms. of urethane during a period of seven weeks. He then developed bilateral gynecomastia presumably due to increased estrogenic substances which the damaged liver was unable to destroy and increased urobilinogen excretion. The gynecomastia slowly decreased after cessation of urethane therapy.

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numerous reports of intolerance to this drug. Curtis observed three deaths following this therapy. The symptoms which should be considered as "danger signals" are: fever, hepatomegaly, nausea, vomiting and a decrease in leukocytes. This drug appears to benefit mycosis fungoides and Hodgkin's disease more than other lymphomatous diseases, just as nitrogen mustard does. Mitchell (243a) described a patient who failed to improve with this form of therapy.

Folic Acid Antagonists. Folic acid antagonists are used only for the treatment of acute diseases, particularly acute leukemia, and therefore do not have much practical value in the treatment of chronic diseases such as mycosis fungoides. Lincoln (212) described a patient who was given teropterin (sodium steroyl triglutamate) by intramuscular injection in doses of 10 mgm. daily for one week and 20 mg. for the next three weeks, but no improvement resulted from this therapy.

Steroids. Derot *et al.* (82) reported temporary improvement in two cases of mycosis fungoides treated with steroids. Goldman (135a) noted favorable results following the local injection of 17-hydroxy corticosterone (compound F) and the topical application of radioisotope SR 90 to the cutaneous nodules and superficial lesions.

Tulipan (341) reported a 57 year old man who had fine scaly erythematous cutaneous plaques of "half dollar to silver dollar" size, with a few scattered excoriations fairly well distributed over the entire body. Subsequently eczematoid patches, semi-circular infiltrated plaques and nodules appeared and bilateral inguinal and axillary lymphadenopathy occurred. He was given 25 mg. of adrenocortropin (ACTH) in 2 cc. saline solution by intramuscular injection every six hours until a total dose of 650 mg. had been given over a period of seven days. There was marked decrease in the pruritus and infiltration of the lesions within two days and each subsequent day the lesions appeared flatter, less infiltrated and became covered with fine scales. He had no untoward reactions to the drug but one week after discontinuance of therapy the pruritus recurred and the lesions became infiltrated. All the lesions subsequently reappeared.

considerably following the third injection All the cutaneous lesions had cleared after 10 injections but a few new, mildly pruritic lesions appeared two months later A second course of "light" injections was then given and there was no further relapse

Chaulmoogra Oil. Because of the reticuloendothelial system involvement in mycosis fungoides, as well as in leprosy, chaulmoogra oil has been advocated for the treatment of mycosis fungoides This treatment was originally suggested by Lomholt (215) and has been used extensively in the United States by O'Leary (258a, c, d, g) He found the results to be encouraging in the first few cases treated but time and final results, in a larger series of cases, were not encouraging

Testosterone. The use of testosterone for the treatment of mycosis fungoides was reported by Garb and Wise (122f) Their patient showed marked improvement, with regression of bullae, a few days after treatment In a later report, Garb (122a) stated that this patient had a flat sugar tolerance curve, lowered blood chlorides, increased ratio of urea nitrogen to nonprotein nitrogen in the blood, low 17 ketosteroid content vitamin C deficiency, increased blood viscosity and positive Robinson, Power and Kepler procedures The bullous lesions had responded well to testosterone propionate therapy, indicating adrenal insufficiency, which was either secondary to the mycosis fungoides lesions or, possibly, the pathologic cause of the disease, Garb stated

Post and Lincoln (277) administered male hormone therapy for a brief, intensive period to patients having mycosis fungoides A dose of 50 mg was given daily for 10 days but failed to influence the disease One man in this series was given estrogenic hormone but also received no benefit from this treatment

Paraaminobenzoic Acid Curtis (73a) believed that the remission in lymphomatous diseases is longer when sodium or potassium paraaminobenzoic acid is administered than with nitrogen mustard therapy However this treatment is only palliative, does not benefit all patients equally and there are

vantage of oral therapy to be the frequency of gastrointestinal reactions Its marked dermatropic fixation of As 76 restricts the indications to the pruriginous and cutaneous form of lymphomatous diseases

Hyperpyrexia Induced fever (malaria typhoid vaccine or hypertherm) or fever from an intercurrent infection have been widely used in the treatment of mycosis fungoides This subject was thoroughly reviewed by Klauder (184b) in 1936 and there has been little change regarding this type of therapy since his publication The favorable influence of an acute infection on mycosis fungoides was first recorded by Bazin (17a) He described a 60 year old man who had numerous cutaneous tumors of mycosis fungoides which began to decrease in size and disappeared within eight days during an attack of erysipelas The lesions healed within the next several months but ten years later the manifestations of mycosis fungoides reappeared

Klauder (184b) stated that nonspecific protein therapy such as typhoid injections and Bacillus coli vaccines have also been used but the results have not been satisfactory He treated one patient having mycosis fungoides with malaria and another with the Kettering hypertherm He found reports of five cases treated with inoculation malaria The results were favorable in four and he concluded that although malaria therapy does not "cure" mycosis fungoides it does produce a distinct effect upon the disease which is greater than with arsenic and roentgenotherapy

A patient having extremely large cutaneous tumors which greatly diminished in size within four days after onset of an acute systemic infection was reported by McVail *et al* (225) The temperature ranged from 100 to 105 6 F for eight days The symptoms of mycosis fungoides were favorably influenced for several months after the infection but there was a relapse five months after the onset of the infection and the patient died

Galloway and MacLeod (120) described a woman who had the erythematous stage of mycosis fungoides During and subsequent to an attack of influenza "The progress of the

Radioactive Isotopes. It is possible that therapy with radioactive isotopes may prove to be of benefit in mycosis fungoides The standard dose is about 30 millicuries which is approximately equivalent to 40 r of total body irradiation Half of this dose may be repeated in four to five days

Radioactive phosphorus was used by Miller (242) and Stratton (325a) The half-life of radioactive phosphorus is 15 days, and for radioactive sodium 14 8 hours Correspondingly, less radioactive phosphorus than radioactive sodium is required because of the difference in the half-life of these two substances, and, the interval between doses is longer for phosphorus than for sodium When available, radioactive sodium is preferable to phosphorus Phosphorus is deposited largely in the bone marrow, and it exerts greater effect here, while *sodium is distributed more uniformly throughout* the body In a case with exuding lesions, radioactive sodium is carried in the blood stream through the lesions to the skin surface, and thus exerts considerable specific effect When obvious or suspected visceral lesions of mycosis fungoides are present, the radioactive substances appear, theoretically at least, to have a definite advantage over roentgenotherapy

Two patients having advanced stages of mycosis fungoides with widespread lesions were reported by Larsson (199) They were given unusually large doses of P 32 which resulted in remission of the disease Investigations have shown that the lesions of mycosis fungoides have a relatively high uptake of P 32, seven to 20 times as much as that of normal skin Larsson emphasized that P 32 therapy is merely palliative for mycosis fungoides, just as is all present day treatment

It would appear that radioactive arsenic would be the drug of choice since arsenic is deposited in the skin Block *et al* (35b) were the first to use radioactive arsenic for the treatment of lymphomatous diseases in 1949 Mallet *et al* (231) used As 76 as a solution of sulphur arsenite Two patients, having terminal stages of mycosis fungoides had improvement of the cutaneous lesions following this therapy and survived for four and six months, respectively They believed the main disad

vantage of oral therapy to be the frequency of gastrointestinal reactions. Its marked dermatropic fixation of As 76 restricts the indications to the pruriginous and cutaneous form of lymphomatous diseases.

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A patient having extremely large cutaneous tumors which greatly diminished in size within four days after onset of an acute systemic infection was reported by McNail *et al* (225). The temperature ranged from 100 to 103.6 F for eight days. The symptoms of mycosis fungoides were favorably influenced for several months after the *infection* but there was a relapse five months after the onset of the infection and the patient died.

Galloway and MacLeod (120) described a woman who had the erythematous stage of *mycosis* fungoides. During and subsequent to an attack of influenza "The progress of the

disease seemed to be arrested, the pruritus diminished, and the scaliness disappeared, and the erythroderma became less vivid." Three months following the influenza, the mycosis fungoides recurred and ten injections of Coley's serum were given which caused regression of some of the lesions. Two patients who improved following an attack of erysipelas were reported by MacCormac (226). One 59 year old patient who developed the tumor stage of mycosis fungoides 17 years previously was alive 12 years after the attack of erysipelas.

However, the patient described by Kaposi (176b) failed to improve following an attack of erysipelas and he mentioned a similar case observed by Vidal (346b).

Symptomatic Therapy. General systemic supportive measures such as transfusion of whole blood for anemia, judicious sedation and adequate diet with good vitamin intake are necessary adjuvants in the treatment of mycosis fungoides.

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PART TWO

HODGKIN'S DISEASE

I.

INTRODUCTION

HODGKIN'S DISEASE is a systemic disease of the reticuloendothelial system which may present a great variety of clinical signs and symptoms. Since the reticuloendothelial system is generalized within the entire body and is predominant in, but not confined to the lympho-hemopoietic system, Hodgkin's disease may arise primarily pathologically as well as clinically in the skin or in any other body tissue. The cutaneous eruption may precede all other symptoms including lymphadenopathy by many months or years and may be the first manifestation of the disease. Hodgkin's disease should not be regarded as a disease manifested by lymphadenopathy and splenomegaly with occasional deposits in other viscera accompanied by a severe secondary anemia. It is a specific lymphomatous disease with protean manifestations in which any tissue or organ of the body may become affected.

In 1832 Thomas Hodgkin (152) wrote "On Some Morbid Appearances of the Absorbent Glands and Spleen" in which he described the pathological aspects of a syndrome consisting of superficial lymphadenopathy associated with hepatosplenomegaly resulting in anemia, cachexia and death. The clinical features of Hodgkin's disease as recognized at the present time were first described by Wilks (345a, c). However Wilks magnanimously designated this entity "Hodgkin's Disease."

Cutaneous manifestations occurring in Hodgkin's disease were first noted by Hutchinson (157) in 1875 when he described numerous tumors varying in size from a millet seed to a walnut . . . for the most part situated beneath the skin." In 1888 Osler (218) stated that the "skin may be the seat of adenoid growths. . . . The growing tumors may involve it and ulceration may occur."

occurred and were then mistakenly believed to have originated in the peripheral regions

The breast appears to be an unusual site of involvement since Adair *et al* (3) who described five such cases were able to find only eight previous reports in the literature One of their patients developed a breast lesion during the course of Hodgkin's disease Another patient a 27 year old man developed a diffuse infiltration of the entire breast which soon responded well to therapy Two patients had nodules in the breast one presented diffuse enlargement of the entire breast and another a large mass in the breast Although the histology of the breast lesion was diagnostic in only one case they believed that the presence of definite masses or infiltration of the breast which respond to roentgenotherapy, is strong evidence of this involvement

D Trauma

There are reports of patients who developed the first symptoms of Hodgkin's disease following trauma Such cases described by Geronne (119) W Bloch (35) and L. B Goldman (124a) developed a hematoma after trauma which was followed shortly by regional lymphadenopathy The lymph node histologic changes were characteristic of Hodgkin's disease

The simultaneous occurrence of Hodgkin's disease and generalized blastomycosis was reported by Mumme *et al* (236) They considered Hodgkin's disease to be the *primary disease* although other investigators have emphasized that some *forms* of mycotic infection may cause this disease The *relationship* between brucellosis and Hodgkin's disease was pointed out by P B Parsons and Poston (253)

Two cases in which trauma was a factor were described by Lovgren and Westman (202) The first patient a 47 year old man had pinched his thumb and a few days later the surrounding area became inflammed and contained pus He developed red streaks on the arm and axillary lymphadenopathy The thumb nail was removed and the symptoms disappeared after

II.

ETIOLOGY

A. Incidence

There appears to be an increase in the number of report Hodgkin's disease in the past 25 years which some investigat believe is due to greater practice of histologic examinatic Apparently there is no predilection for any race or co However, the disease affects men more frequently than wom The onset appears to be more frequent in the third decade life

B. Portal of Entry

It was the opinion of Symmers (320) that the portal of ent is never through the skin but rather through the mucous mem branes, particularly the gastrointestinal tract However, t infectious agent was believed to have entered through wound in the skin in the cases reported by Clarke (63), Hau (138), Hendricks (146a, b), Kren (178b) and Sisto (303)

C. Sites of Involvement

Because Hodgkin's disease is histologically a reticuloend thelial system disease it may occur in almost any organ of th body The peripheral lymph nodes are most frequently in volved In a survey by Merner and Stenstrom (218) th disease was found to have begun in the cervical lymph node in 60 5 per cent and in the axillary lymph nodes in 10 3 per cen of the cases Primary cutaneous involvement, including thos having pruritus as the first symptom occurred in nine cases Many cases originating in deeper areas such as the abdomen were not detected until peripheral lymph node involvement

occurred and were then mistakenly believed to have originated in the peripheral regions

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The simultaneous occurrence of Hodgkin's disease and generalized blastomycosis was reported by Mumme *et al* (236) They considered Hodgkin's disease to be the primary *disease* although other investigators have emphasized that some forms of mycotic infection may cause this disease The *relationship* between brucellosis and Hodgkin's disease was pointed out by P B Parsons and Poston (253)

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one month However, the lymphadenopathy persisted and several weeks later the lymph nodes began to enlarge, became tender and were sometimes painful The patient died 11 years later and, at autopsy, lesions from the liver and spleen the mediastinal, axillary and inguinal lymph nodes and the skin from the left axilla, showed the histologic picture of Hodgkins disease The second patient was a 64 year old woman who injured the femur, just below the groin The lesion healed and caused no further symptoms until a painful boil" appeared in the cicatrice three years later The surrounding skin became increasingly reddened, infiltrated and edematous There were several rounded, firm, tender papules, some the size of a "half walnut,' involving a 'palm' sized area just below the groin Histologic examination revealed an inflammatory cell infiltration with new growth of connective tissue in the cutis and sub cutis The epithelium was intact The infiltrated cells consisted of plasma cells and other round cells, partly leukocytes and one or two giant cells The skin became generally dry, shiny and exfoliated, while the legs were cyanotic and showed increased vascular delineation The papules became ulcerated and a lamellar eruption involved the legs The cutaneous eruption on the thigh improved following roentgenotherapy but the tumor of the iliac fossa was unchanged

III.

PATHOGENESIS AND PATHOLOGY

Pathogenesis

The theories concerning the nature of Hodgkin's disease include neoplasm, inflammation, metabolic abnormality and a condition midway between inflammation and neoplasm. None of these theories has been proved and the disease has never been produced experimentally in animals.

In general, hypotheses fall into one of the following major groups listed by *Hoster* and *Dratman* (*154c*):

1) Neoplasm
   a) Of myeloid origin (reticulum cell, megakaryocyte)
   b) Of lymphoid origin (reticulum cell, lymphocyte)
2) Inflammation
   a) Infectious origin
   b) "Toxic" origin
   c) Allergic origin
3) Midway between inflammation and neoplasm
   a) Hormonal imbalance
   b) Other metabolic imbalance
   c) Autonomic nervous system imbalance
   d) Allergy

1. Neoplasia. Hodgkin's disease is a neoplastic disease of the reticulum, most probably a slowly progressive form of the large cell (reticulum) lymphosarcoma according to Sweitzer and Winer (319b). Some investigators believe that Hodgkin's disease, mycosis fungoides and lymphosarcoma are biologically, morphologically and clinically variants of the same disease. However, we are in accord with Wallhauser (333) and others

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who believe that in the absence of known etiologic agents adherence to strict histological distinction should be continued.

2 *Inflammation* A case which was highly suggestive of infection was described by Bersack (27c) This man's initial cutaneous lesions were small erythematous areas about 0.5 cms in diameter present "in hundreds over the entire body" They soon became slightly raised circumscribed and finally nodular and new crops of lesions were accompanied by a rise in temperature Histologic study of the early lesions indicated a normal epidermis with minimal reaction consisting of endothelial and fibroblastic proliferation about vessels and an increase in the number of lymphocytes in the corium However the histologic picture of the older cutaneous lesions indicated Hodgkin's disease At autopsy miliary Hodgkin's disease was present in the serous surfaces lungs mucosa of the respiratory tree pericardium spleen testes and the capsule of the pancreas The abdominal and pelvic lymph nodes were involved in the process Since "no malignant cells were found in the microscopic examination of the early skin nodules" Bersack considered that this finding favored the infectious nature of the disease

The experiments of Perk Lee Davis were described by Hoster (154a) Chest fluid was withdrawn from a patient having terminal Hodgkin's disease with pulmonary and pleural lesions and was injected intramuscularly into the donor and two other patients with advanced Hodgkin's disease At the end of 48 to 72 hours all three patients developed a generalized severely pruritic cutaneous eruption followed by vesicle formation Although the generalized dermatitis began to disappear after three or four days a few lesions in certain areas became large and appeared as nodular vesicular or ulcerative tumefactions These lesions revealed the typical histopathology of Hodgkin's disease The lesions responded well to roentgenotherapy but not to chemotherapeutic agents The patients pursued a rapid downhill course following inoculation suggesting that their disease had been accelerated A similar report of somewhat less widespread dissemination of

cutaneous lesions following roentgenotherapy over an involved spleen suggests autoinoculation from a disrupted focus according to Hoster

Wiseman (350) believed the infectious theory of Hodgkin's disease was not necessarily in conflict with the fact that certain cases exhibit definite neoplastic characteristics The phenomena of neoplasia arising in chronic lesions is not unusual in other tissues of the body When neoplastic transformations occur in lymphoid tissues however the cell primarily involved is definitely not the lymphocyte as suppression of lymphopoiesis is an outstanding feature of this disease Hodgkin's disease therefore while a disease of lymphatic tissues does not appear primarily to affect the lymphocyte itself

While some investigators (Chevallier and Bernard 62 Grossman and Schlemmer 132) consider mycosis fungoides and Hodgkin's disease to be variants of the same disease most dermatologists believe that these two diseases are separate entities (Arndt 9b Arzt 10e)

Pathology On gross examination the lymph nodes are found to be of a fleshy or fibrous consistency and tend to remain discrete seldom matted together On section areas of caseous necrosis are frequent and although this necrosis is actually due to the disease itself this finding has led to the suggestion of tuberculosis as the causative agent Lymphadenopathy with obliteration of the sinusoids is of great diagnostic importance The areas of necrosis can be distinguished from tuberculosis by their sharp demarcation from the surrounding tissue and the absence of epithelioid cells Often there are large numbers of eosinophil leukocytes in the cellular areas

✓ The microscopic picture varies widely in different cases and sometimes in various lymph nodes in the same person There may be some structural differences related to the stage of the disease The earliest change in the lymphoid tissue is proliferation of reticulum cells increased numbers of mitoses and dilatation of blood vessels and lymph sinuses As the process develops proliferating reticulum cells and lymphocytes fill the

lymph and reticular spaces, obliterating any distinction between follicles and sinuses. During this proliferative period giant cells, plasma cells and eosinophils may appear in large numbers. The established lesions form a mass of lymphocytes, endothelial cells, Langhan's giant cells, Sternberg-Reed cells, lymphoblasts, myelocytes and megakaryocytes. Rae (267) described a case with pruritus in which the connective tissue of the skin was infiltrated by lymphocytes.

The distinctive features of Hodgkin's disease consist of an increase in the number and size of the reticulum cells, often with the formation of Sternberg Reed cells, increase of reticulum fibers with the formation of areas of fibrosis, obliteration of the sinusoids, eosinophils, areas of necrosis and increase of lymphoid cells. Typical cases show Sternberg Reed cells and areas of fibrosis. Jackson and Parker (159f) would restrict the diagnosis of Hodgkin's disease to cases showing Sternberg-Reed cells although Bersack (27a) stated that these cells are present only in later stages of the disease. Careful examination has often failed to disclose Sternberg Reed cells but later studies, after further progression of the disease, has revealed the typical findings.

Three types of Hodgkin's disease, each having a distinct pathologic appearance and a different prognosis, were described by Jackson and Parker (159f). *Paragranuloma* is described as the early variety, its main feature being lymphoid hyperplasia and the principal cell the adult lymphocyte. Sternberg Reed cells are present in small numbers. This type is considered to be rather benign but it may progress to Hodgkin's granuloma. The distinguishing features of the granuloma group are eosinophilia, necrosis and fibrosis. This type is the one most frequently seen in clinical practice and presents a grave prognosis. *The third type, Hodgkin's sarcoma*, is highly malignant. The principal findings are large tumor cells and Sternberg Reed cells with only occasional necrosis and relative rarity of the characteristic cells present in the granuloma type. It is usually primary in the retroperitoneal lymph nodes and gastrointestinal tract and rather uncommon in the peripheral lymph nodes.

The reticulum fibers are invariably increased in Hodgkins disease In some cases the increase in fibers is found so evenly distributed throughout the node that there is no evidence of the original location of the sinuses but in most cases the newly formed fibrous tissue is more dense at the periphery of the follicles and in the region of the blood vessels The reticulum fibers gradually develop into collagenous fibers which are usually first formed in these same areas i e the periphery of the follicles and around blood vessels according to Jackson and Parker (159f) This increase in reticulum fibers is an aid in differentiating Hodgkins disease from leukemia and lymphosarcoma In neither of the two latter conditions is there much increase in reticulum fibers in fact because of the increase of free cells the fibers seem fewer than normal

The earliest detectable change in lymphoid tissue is said to be a proliferation of reticulum cells with increased mitoses in these cells Jackson and Parker (159f) described this proliferation as accompanied by dilatation of blood vessels and lymph sinuses As the process advances the lymph and reticular spaces become filled with proliferating reticulum cells and lymphocytes with obliteration of the distinction between follicles and sinuses During this proliferative period large epitheloid cells with vesicular nuclei appear as may also giant cells with one or more nuclei and prominent nucleoli Occasionally very large giant cells with many small nuclei peripherally arranged are seen Plasma cells are found in large numbers and eosinophils are often abundant except in the germinal centers It is not uncommon however to observe a lymph node in which few or no eosinophils are present There may be a marked multiplication of connective tissue cells resulting in their numerical predominance Areas of ischemic necrosis and hyalinized fibrous tissue may be noted

Jackson and Parker (159f) believed the histologic appearance to be highly significant in the prognosis of Hodgkins disease However this is disputed by a number of investigators including Slaughter and Craver (307) who reported 14 cases of Hodgkins sarcoma five of whom survived for more

lymph and reticular spaces, obliterating any distinction between follicles and sinuses. During this proliferative period, giant cells, plasma cells and eosinophils may appear in large numbers. The established lesions form a mass of lymphocytes, endothelial cells, Langhan's giant cells, Sternberg-Reed cells, lymphoblasts, myelocytes and megakaryocytes. Rae (267) described a case with pruritus in which the connective tissue of the skin was infiltrated by lymphocytes.

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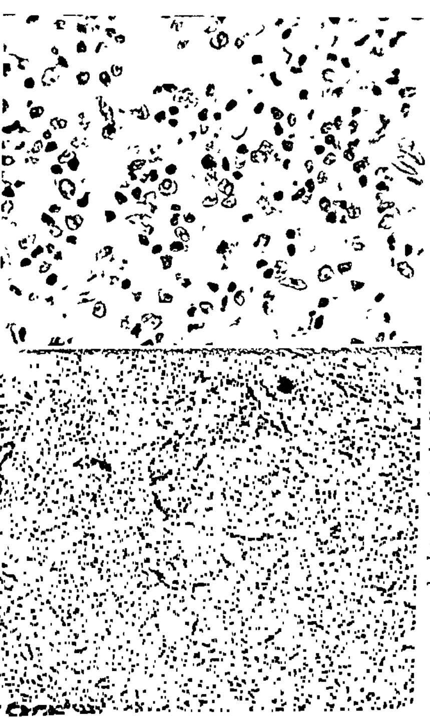
than three years and three of these five survived for more than five years and one for over seven years They noted no consistent histologic picture in the patients who survived for less than six months

Fraser and Mckie (107c) outlined the histopathologic evolution of Hodgkin's disease as follows 1) proliferation of reticuloendothelial lymphocytic tissue 2) disturbance and disruption of the natural evolution and development of the "lymphoreticulo-endothelial group" of cells so that many cells of immature type appear, 3) development of the following cellular elements eosinophils, multinucleated cells and large mononuclear cells, 4) conversion or "degeneration of cell elements into fibrous tissue"

Hodgkin's disease presents the same essential histologic characteristics wherever it is found Certain special characteristics of cutaneous lesions should be noted In a case cited by Bersack (27c), in which there was terminal miliary spread to the skin the histologic study of early cutaneous lesions had revealed a normal epidermis with "minimal reaction" about several small blood vessels The changes consisted of slight endothelial and fibroblastic proliferation A moderate number of lymphocytes were distributed throughout the corium Histologic examination of the cutaneous lesions, at a later date revealed Hodgkin's disease When the typical cutaneous lesions have become established, further changes consist of greater diffusion and tumefaction and more necrosis, according to Beimann *et al* (271)

Histopathology of the Skin

In true Hodgkin's disease of the skin the cutaneous histopathologic changes are similar to those present in the lymph nodes Just as in mycosis fungoides, the infiltrate is composed of a multiplicity of cell types without however pyknosis and karyorrhexis of individual cells Typical sections show a rich granulation tissue characterized by numerous giant cells which were originally described by Sternberg and by Reed The granulation tissue consists of an indefinite tumor mass present



1. Increase of reticulum fibers in Hodgkin's disease (reticulum stain)
2. Multiplicity of cell types

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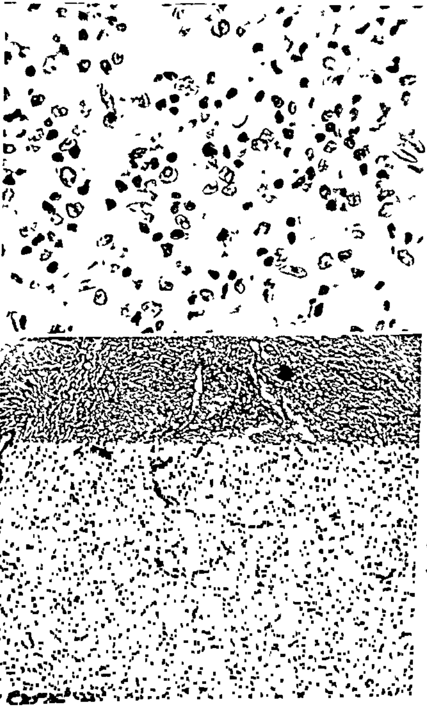
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1 Increase of reticulum fibers in Hodgkin's disease (reticulum stain)
2 Multiplicity of cell types

in the cutis and upper portions of the subcutis The upper limits of this mass are evenly outlined but the edges and lower borders are arranged in oval or round nodes which are sharply demarcated from one another by broad bands of normal or edematous and hyaline degenerated connective tissue The mass is characterized by its polymorphous composition as well as by its nodular configuration

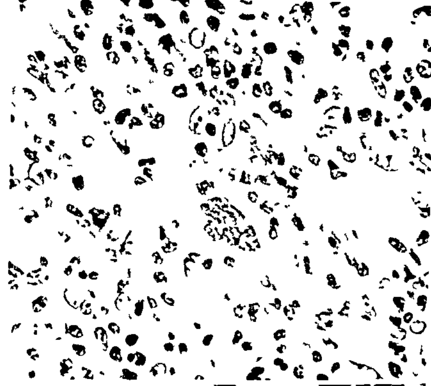
This polymorphism is dependent upon the different cell types comprising the infiltrate as well as upon the distribution of these cells in individual nodules in the cutis The latter may be composed entirely of any one type of cell or of all of the following various cells making up the infiltrate

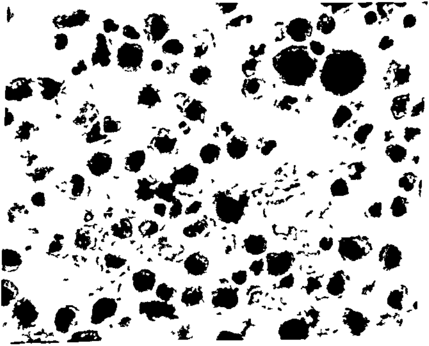
1) Numerous small lymphocytes Round cells of uniform size having a deeply staining nucleus which may or may not have a very narrow homogeneous basophilic protoplasmic body These cells may be diffusely scattered throughout the tumor or they may lie in collections such as those present in lymph nodes

2) Large lymphocytes (lymphoblasts) These cells are less numerous and more evenly distributed and are two to three times the size of the small lymphocytes They are regularly round or oval in shape with a central eccentric round or oval pale staining nucleus which is present in an easily recognizable granular protoplasm

3) Plasma cells Some cases present numerous plasma cells while in others they are few in number They are of polygonal shape with a protoplasmic body which has a marked affinity for basophilic stains Their nuclei are eccentric partially surrounded by a clear space and the arrangement of the chromatin resembles the spokes of a wheel

4) Fixed connective tissue cells There is a marked proportion of these cells which vary greatly in size and shape They may be spindle shaped drawn out at both poles or branched and contain pale vesicular like nuclei Larger forms of fibroblasts may be present in the connective tissue separating the individual nodes of infiltration Occasionally a connective





3 Granulation tissue showing a Sternberg Reed giant cell in center

4 Sternberg Reed giant cells (upper right hand corner)

tissue cell having a definite spindle shape and five or six nuclei may be present in newly formed connective tissue

5) The Sternberg Reed cells * These characteristic cells are of reticular origin and are diagnostic of Hodgkins disease These large uni nucleated or poly nucleated cells are present between plasma cells lymphocytes proliferating connective tissue cells or they may appear alone in small nests in some areas giving the tissue a sarcomatous appearance They vary considerably in shape they may be round oval rhomboid or polygonal and occasionally have an elongated spindle shape The deeply staining nucleus usually present in the center of the cell, may also vary greatly in size and shape It may be round oval or kidney shaped and has been described in the form of a "corkscrew" "horse shoe" "open ring" or whorl These cells are in the process of active proliferation for they contain many mitotic figures Prominent nucleoli having large coarse irregular chromatin granules are also present Sternberg Reed cells must be distinguished from the clumped endothelial or reticulum cells forming the pseudo-giant cells of mycosis fungoides

6) Mast cells These round or spindle shaped cells have a granular cytoplasm and a regular round pale nucleus but are not numerous

7) Polymorphonuclear neutrophils These cells are not abundant

8) Eosinophils They are usually present in large numbers in the infiltrate particularly in the deeper layers of the cutis and upper portions of the subcutis in the vicinity of the blood vessels However eosinophils are not a constant finding

The elastic tissue is completely destroyed within the infiltrated areas except for the elastic membrane of the blood vessels which remains intact The blood vessels are dilated and contain red blood cells and small lymphocytes The endothelium of the vessels is usually proliferated in the tumor

* See Ill strat ons 3 and 4



5 Edematous and hyaline degenerated connective tissue
6 Polymorphous cell composition in a nodular lesion

IV.

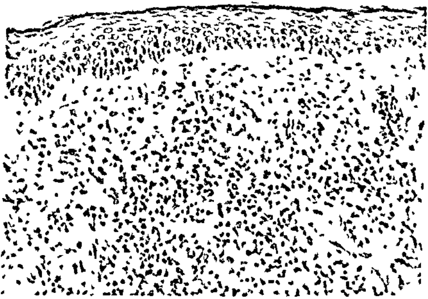
SYMPTOMS

A General

In the majority of cases Hodgkin's disease progresses through three stages 1) A latent period during which the lymph nodes enlarge without symptoms 2) a period of progression and generalization during which symptoms of varying severity appear and 3) a period of cachexia preceding death One of the distinguishing characteristics of Hodgkin's disease is the changing course of symptoms week by week and month by month Spontaneous remissions and exacerbations occur in the early stages and no patient experiences all of the symptoms described

The symptoms are variable depending upon the stage of progression at the time of examination The only complaint may be palpable cervical or axillary lymph nodes Hoster and Dratman (154c) found the presenting symptoms to be painless progressive enlargement of a lymph node or nodes in 79 per cent of the cases The first indication of mediastinal lymph node involvement may be a dry "hacking" type of cough Obstruction due to marked mediastinal enlargement or extension of the lesions into the pulmonary parenchyma will later cause dyspnea cyanosis and dysphagia and result in venous engorgement

Thirteen patients described by L B Goldman and Victor (124b) had involvement of the sternal lymph nodes In nine the enlargement was to the right and in four to the left of the edge of the sternum along the course of the internal mammary artery and at the level of the second and fourth intercostal spaces These lymph nodes measured from 6 to 10 cms and were fixed to the underlying chest wall They found these



7 Epidermis is not involved but is atrophic due to underlying tumor mass

The epithelium, as a rule, is not affected but is usually thinned and atrophic due to the underlying tumor

The early specific changes in Hodgkin's disease reveal an increase in lattice fibers,* just as in mycosis fungoides

* See Illustration I

Pruritus is discussed in more detail under the nonspecific cutaneous lesions (See Chap V p 240)

W Bloch (35) has shown that an allergic history is a rather frequent occurrence in leukemia This allergic history has occasionally been described in Hodgkins disease The child reported by Limper (192) had asthma purpura angioneurotic edema measles and pertussis Hodgkins disease followed an attack of herpes zoster A child reported by Stewart (313) was asthmatic and had a family history of allergy The child described by Klawins (173) had long standing pruritic eczema A year old child who had furunculosis scabies eczema impetigo pyelitis and phlyctenular conjunctivitis preceding the development of Hodgkins disease was reported by L F Barker (16) Seborrheic eczema preceding Hodgkins disease was described by MacCormac (207b) and Hoster and Doan (154b) reported a 26 year old woman who had urticaria since childhood and whose paternal grandmother had allergic asthma

B Hemogram Hemoglobin and Red Blood Cells

The hemoglobin value and red blood cell count may be normal in the early stages of Hodgkins disease A mild normochromic or microcytic anemia usually appears during periods of exacerbation and as the disease progresses A macrocytic anemia with or without achlorhydria is occasionally noted The anemia frequently becomes progressively more severe as the disease progresses and becomes refractory to all treatment in the terminal stages of the disease

White Blood Cells The white blood cell changes though often marked are believed to be neither constant typical nor diagnostic of Hodgkins disease There is seldom any constant correlation between the clinical picture and the white blood cell count Jackson (159a) and Wiseman (350) believed that a definitely elevated white blood cell count indicated that the disease process was widespread.

The significance of the eosinophilic reaction *in Hodgkins* disease is not known but has been attributed to either an un

prominences to be pathognomonic of Hodgkin's disease just as Virchow's node is indicative of an intraabdominal malignancy

Other symptoms, in order of frequency, were found by Hoster and Dratman (154c) to be loss of weight and appetite, weakness, fever, pruritus, cough, and dyspnea Frequent coincident infections such as tonsillitis, upper respiratory infections, otitis media, and mouth infections may occur Not infrequently, weakness is the first symptom and when not accompanied by obvious lymphadenopathy, careful search for enlarged nodes and abdominal masses is indicated, or the characteristic lesions may be demonstrated by roentgenograms of the chest

Fever may occur without obvious relation to the enlarged lymph nodes, which may increase in size during an episode of fever Pulmonary involvement is often accompanied by fever Pain, particularly back pain, is frequent in patients who do not have fever and usually results from enlarged retroperitoneal lymph nodes Hoster and Dratman (154c) believed that backache is sufficient indication for roentgenotherapy of the retroperitoneal region, even in the absence of other positive signs of Hodgkin's disease Pain usually occurs in bone lesions before they are demonstable roentgenologically although large bone lesions, without symptoms, have also been described

Paraplegia appears to be the most frequent neurologic symptom and paralysis of one or both lower extremities occasionally results from vertebral or extradural involvement However, collapse of the vertebrae may occur without paralysis

Nausea and vomiting are not necessarily indicative of involvement of the gastrointestinal tract but are explained by the toxic effects of the disease Hemorrhagic diathesis may precede melena and hematemesis

Pruritus may be an early and distressing symptom and is occasionally the presenting symptom It may be severe and marked excoriations from scratching may be present There is often no characteristic histologic change, although there is frequently some degree of lymphocytic infiltration in the cutis

tissue is that seen in chronic toxic states The panhyperplasia of the bone marrow simulates that of Bantis disease (splenic anemia) A pathologic type of megakaryocytopoiesis involving the lymphoid megakaryocytes is observed in some cases of Hodgkins disease These produce atypical forms of platelets The finding of increased numbers of normal or atypical plasma cells eosinophils and reticular cells is neither a constant nor specific pattern of the bone marrow in Hodgkins disease They found that eosinophilia of the bone marrow cannot be correlated with the peripheral blood eosinophilia The accurate diagnosis of this disease is established only by the histologic finding of the specific pleomorphic lesion which is best found in the involved lymph node The finding of any one cell or group of cells in aspirated sternal bone marrow is insufficient evidence for the diagnosis of Hodgkins disease

known chemotactic substance present in the involved lymph nodes, necrosis of the nodes, reaction to roentgen rays, splenic involvement or an allergic response, according to Hoster and Dratman (154c) An eosinophilia was present in 15 to 20 per cent of their cases Rare cases, having more than 100 000 eosinophils per cu mm of blood, were described by Major and Leger (211) and Stewart (313) Although the peripheral blood and bone marrow changes are not specific, the characteristic blood picture is suggestive of Hodgkin's disease in some cases, according to Wiseman (350) He stated "Given a blood study that shows a lymphoemia with a high monocyte leukocyte index with normal total white blood cells, a mild neutrophilia and any increase in eosinophils, one would appear to be justified in suggesting the possible diagnosis of Hodgkin's disease on the basis of blood examination alone I have observed no other disease, save an occasional case of tuberculosis, that gives this blood picture"

Blood Platelets. The circulating blood platelets are usually increased, often to levels of 3,500,000 per cu mm, in untreated cases, particularly early in the disease Low blood platelet counts, associated with a hemorrhagic and purpuric diathesis, are rarely the presenting symptom of the disease (Simonds 301), and appear to result from over-exposure to roentgen rays, terminal disease of hypersequestration of platelets by the spleen or associated with septicemia

The Erythrocyte Sedimentation Rate. In Hodgkin's disease there is usually an elevated sedimentation rate during periods of disease activity Following effective palliative therapy and during periods of remission, the sedimentation rate becomes more normal This test is suggested as useful in following the course of the disease and as a guide to therapy The sedimentation rate may be normal during the early stages of Hodgkin's disease

Sternal Bone Marrow After studying the sternal marrow in cases of Hodgkin's disease Limarzi and Paul (191b) stated that the most constant finding was myeloid and megakaryocytic hyperplasia The morphologic pattern of the granulopoietic

The cutaneous manifestations of the nonspecific or toxic group are varied and one group of symptoms commonly associated with Hodgkin's disease has been referred to as the eleven "Ps" pallor, pruritus, prurigo-like papules, pigmentation pyoderma, purpura, pemphigoid lesions, posterior root spinal ganglionitis (herpes zoster), pityriasis rubra (exfoliative dermatitis), phlebitis and poikilodermatomyositis (Bluefarb 36b) A complete list of the nonspecific cutaneous lesions, however, would include the following

1) Pruritus, with or without excoriations, pyoderma and lichenification
2) Prurigo-like papular lesions
3) Pigmentations, including jaundice
4) Urticaria and erythematous lesions (scarlatiniform and morbilliform, increased perspiration)
5) Erythema multiforme and erythema nodosum like lesions
6) Eczematoid and psoriasiform lesions
7) Erythroderma and exfoliative dermatitis
8) Bullous and pemphigoid lesions
9) Herpes zoster and herpes simplex
10) Purpuric and hemorrhagic lesions
11) Edema and lymphedema (elephantiasis)
12) Trophic changes
    a) Alopecia
    b) Icthyosiform lesions and hyperkeratosis of palms and soles
13) Dermatomyositis
14) Phlebitis
15) Miscellaneous rare toxic lesions

These nonspecific cutaneous lesions, occurring in association with Hodgkin's disease may precede, accompany or follow the general manifestations of the disease

The frequency of nonspecific cutaneous lesions has frequently been estimated The following figures are a good indication of the frequency

V.

CUTANEOUS LESIONS

THE CUTANEOUS manifestations of Hodgkin's disease are (1) nonspecific or toxic lesions, (2) specific lesions and (3) lymphogranulomatids or "id" reactions

The lesions comprising the first group occur much more frequently than the lesions in the other two groups and consist of lesions which are neither clinically nor histologically pathognomonic of the disease The second group of lesions are the least frequent in occurrence and show the specific and pathognomonic histologic characteristics of the cutaneous disease, characterized by papules, nodules, tumors, ulcers and infiltrations The third group, lymphogranulomatids or "id" reactions, are clinically nonspecific but histologically typical of the disease. They were formerly combined with group one as toxic or "id" reactions but it is our opinion that these groups should be separate and histological distinction be made For example, the term "tuberculid" is used to designate a lesion due to the tubercle bacillus and has the structure of the tuberculous infiltration This also applies to syphilide and lepride, with reference to the treponema pallidum and Hansen's bacillus, respectively Therefore, 'lymphogranulomatid" should refer to a lesion having the cutaneous histologic structure of Hodgkin's disease and this same premise should apply to the "leukamids"

A. Toxic or Nonspecific Lesions

Toxic eruptions associated with Hodgkin's disease were first described by Gowers (128) in 1879 He stated that in addition to pallor there may be 'bronzing of the skin and that . . certain skin diseases are not uncommon during the cachectic period, especially a papular rash on the backs of the forearms and hands, furuncles and pemphigus" He did not however, mention pruritus

marily present only in elderly persons Coarse wrinkles often pronounced appear about the mouth and the skin particularly that of the hands sometimes appears atrophic

2 *Pruritus* Pruritus is by far the most frequent cutaneous manifestation of Hodgkin's disease In a study of 319 patients L B Goldman and Victor (124b) found that "one leading and outstanding symptom was pruritus and various statistics show that it occurs at some time in from 5 to 50 per cent of all cases with an average of 20 to 25 per cent Favre (100a) considered pruritus to be constantly present early in the course of the disease Craver (73a) considered that pruritus occurred in 20 per cent of the cases but later (73c) he estimated that 29 per cent had pruritus Rolleston (275a) believed that pruritus may not be mentioned unless the patient is specifically questioned regarding this symptom and this may account for the low incidence in Longcope's (199) series Pruritus appears to be considered a common symptom among French investigators Poinso *et al* (261) reported three cases of Hodgkin's disease without pruritus or eosinophilia" The following incidence of pruritus occurring at some time in the course of Hodgkin's disease has been described

Writer	Number of Cases	Pruritus Per Cent
Adlercreutz (4) ✓	30	30 0
Bersack (27c) ✓	224	13 4
Burger and Lehman (50a ✓	54	18 5
Burnam (52) ✓	173	31 8
Cole (64a)	34	23 5
Colrat (66)	13	84 6
Desjardins and Ford (80B) ✓	135	6 7
Goldman and Victor (124b	212	11 6
Jackson and Parker (159d) ✓	220	29 0
Longcope (199) ✓	86	3 5
Weinberg (339)	12	58 3
Ziegler K. (361)	70	11 4

Average incidence of pruritus is 26 46 per cent

Writer	Total Cases Hodgkin's Disease	Cutaneous Lesions Per Cent
Barron (18)	24	16
Bersack (27c)	144	17.6
Burnam (52)	173	31.7
Busman and Johnston (53)	37	16
Cole (64a)	33	40
Craver (73c)	226	29
Epstein and MacEachern (94)	156	53.2
Goldman, L. B. (124a)	212	38
and Victor (124b)	319	39
Jackson and Parker (159d)	220	13
Krueger and Meyer (179)	60	41.6
Miller (224a)	55	40
Wallhauser (333)	33	29
Ziegler, K. (361)	70	25

Cutaneous lesions, as the *first* manifestation of Hodgkin's disease, was mentioned as occurring in 10 per cent of the cases by Rulison (283a) and in 5 to 12 per cent by K. Ziegler (361). It would then appear that cutaneous lesions varied from 13 to 53 per cent, with the higher incidence reported by dermatologists. A good average would be from 25 to 35 per cent having cutaneous manifestations and about 10 per cent of the patients presenting cutaneous lesions as the initial symptom.

1. Pallor. The skin may be pale and appear yellowish at first glance. This is not due to jaundice but to the "unmasking" of the underlying yellow of the skin because of lack of hemoglobin. This yellow color may be due, in part, to degenerative changes in connective and elastic tissues. The pallor is usually the result of iron deficiency and there may be associated evidence of iron deficiency, such as glossitis or koilonychia. This usually results from lack of appetite, diminished food intake, difficulty in food assimilation or interference with iron and vitamin absorption, chronic bleeding or hemolytic anemia.

Another characteristic feature of iron deficiency anemia is the wrinkled, thin and translucent appearance of the skin. Even young patients have an atrophic, inelastic, wrinkled skin, ordi

Although it is frequently an early symptom it may appear at any time even late in the course of the disease Rolleston (275a) believed that like other forms of pruritus it may be precipitated by exposure to heat or cold It is usually more intense at night and may be present alone or together with other cutaneous lesions The pruritus appears to be more severe at the onset and during exacerbations of the disease It usually appears on the extremities and trunk although it frequently becomes generalized and may be particularly severe on the back In rare instances it is confined to localized areas

Pruritus without visible cutaneous lesions should always lead to the suspicion of a lymphomatous disease particularly Hodgkin's disease Severe intractable pruritus without specific cutaneous lesions is frequent in Hodgkin's disease whereas it is not common in leukemia and when present is usually associated with a cellular infiltration and erythroderma Because of the severity of the pruritus the skin may be excoriated and this disease must therefore be differentiated from neurotic excoriations scabies pediculosis corporis and senile pruritus Dermographism is sometimes present with pruritus

The reason for this symptom is a disputed question which has given rise to much speculation and discussion Paltauf (249) believed the pruritus due to autointoxication from the absorption of substances (irritating toxins) derived from the altered lymph nodes or as a local reaction to the accumulation of such toxic substances in the skin a theory concurred by Shelmire (298) and Desjardins and Ford (80b) Schaumann (289) stated that pruritus is due to the circulation of products of nuclear decomposition from the excessive breaking up of blood cells in the spleen Other theories which have been advocated include the anaphylactic or irritation of the peripheral nerve endings in which event the toxin must be blood borne and not produced locally since the pruritus often occurs before lymphadenopathy is apparent and is as a rule not localized The rare lymphadenomatous specific cutaneous lesions are usually not pruritic The termination of the sensory cerebrospinal nerves would appear to be irritated but Golay

Pruritus may be the initial symptom in Hodgkin's disease and may precede other symptoms by varying periods of time although it may occur only a few hours before death, as in Collier's (65) case Pruritus, as the initial symptom, is believed by K Ziegler (361) to occur in 5 to 12 per cent of the cases Rolleston (275a) believed that the disease runs a rapid course in patients having initial pruritus Of the 55 patients having pruritus in Burnam's (52) series, it was the initial complaint in 12 Among Weinberg's (339) seven patients having pruritus, it was the initial symptom in three Among 119 patients with initial symptoms referable to abdominal lesions, Minot and Isaacs (227) found that 18, or 15 per cent, had intense pruritus for a considerable period early in the disease However, the incidence of pruritus may have been higher in this series since only the initial symptom was mentioned Of 30 patients having pruritus, Bersack (27b) found the pruritus to be the only symptom in 21 cases

Pruritus, which persisted for three months prior to other symptoms, was described by Falconer and Leonard (98 case 2) in a 37 year old woman The 28 year old man, described by Middleton (221 case 3) and a 41 year old woman, reported by Wright (355 case 2) both had pruritus for eight months before other symptoms appeared Pruritus as the only symptom for one year, was described by Ginsburg (121a case 1) and by Cornbleet *et al* (69) The latter patient had temporary relief of pruritus following a roentgenogram of the mediastinum Ginsburg's (121a case 2) patient, and the 24 year old man described by Ambler (7) both had pruritus for two years prior to the development of other symptoms Rittner (269) mentioned a young woman with Hodgkin's disease who had severe pruritus for two years before mediastinal lymphadenopathy appeared which was followed by cervical lymphadenopathy

The pruritus which may be either localized or generalized, according to Wilhelm and Goeckerman (344), is 'characteristically experienced under the skin The pruritus may be intolerably severe and may be either continuous or intermittent

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(123) suggested that stimulation of the sympathetic nerves causes pruritus. On the other hand it is also attributed to irritation of the central nervous system. Milian and Blum (223b) believed it to be due to spinal radiculitis and compared it to tabetic pruritus because they found lymphocytosis of the spinal fluid. There is little evidence that the toxin is produced in the affected lymph nodes although in Blaschko's (33) case





8. Pruritus with lichenification (Bluefarb and Schwartz, *Arch Dermat*, Feb 1956)

9. Prurigo-like papules of the legs (Bluefarb and Schwartz, *Arch Dermat*, Feb 1956)

a young man with lymphosarcoma of the cervical lymph nodes intolerable pruritus disappeared two days after excision of the involved nodes but subsequent lymphadenopathy recurred without recurrence of the pruritus. However, Cole (64a) reported a case in which pruritus occurred two months after excision of a cervical lymph node. Shelley and Arthur (297) postulated that pruritus may be related to the activation or release of tissue or serum proteinases in the epidermis since proteinases are uniquely pruritogenic.

The association of pruritus with eosinophilia was stressed by Favre (100a) and Colrat (66). Klein (174) emphasized the occurrence of large numbers of eosinophils in involved lymph nodes when Hodgkin's disease is complicated by toxic cutaneous lesions, such as pruritus. Simonds (301) described a woman with extremely irritating cutaneous papules who had large numbers of eosinophils in the lymph nodes. Schlecht and Schwenker (290) and Urchs (329) believed the presence of eosinophils to be an expression of a condition of anaphylaxis. Products of partial protein decomposition originating in the areas of necrosis sensitize the patient and, as a result of local sensitization, the eosinophils are "enticed" into the affected nodes. The pruritic cutaneous lesions are placed on the same etiologic basis by Urchs (329). However, Cole (64a) could not correlate the pruritus with the eosinophilia since the attacks of pruritus accompanied a flare up of the lymphadenopathy in his cases. MacLeod (208b) believed the pruritus to be due to a toxic influence, also responsible for the lymphadenopathy, and in his case the exacerbation of pruritus preceded an increase in lymphadenopathy. He also noted that the pruritus disappeared entirely toward the termination of the disease. Rolleston's (275a) patient had bouts of pruritus associated with lymphadenopathy but he was not able to distinguish any constant relationship between Hodgkin's disease of the viscera and pruritus. Desjardins *et al* (80c) believed that pruritus, with or without toxic or infiltrated cutaneous lesions, indicated lymphomatous invasion (Hodgkin's disease or lymphosarcoma) of the abdominal (retroperitoneal) lymph nodes. As proof, they stated that pruritus diminishes rapidly after thorough irradiation of the abdomen, whereas such a favorable effect is not observed after irradiation of other regions.

In speculating on the character of the toxins causing pruritus, Rolleston (275a) stated that the toxins have been thought to be protein in nature, derived from leukocytic destruction. If this were true, pruritus would be much more frequent and constant in leukemia than in Hodgkin's disease, which is not the case. Furthermore, the occurrence of early pruritus, before

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lymphadenomatous nodes are palpable, shows there is no correlation between the probable amount of cytolysis and pruritus This would suggest that pruritus is due to a toxin responsible for the lymph node enlargement rather than to proteins derived from the destruction of lymphoid cells

Ginsburg (121a) described an unusual case with pruritus of both feet and extending up to the knees, which occurred simultaneously This illustrates how pruritus may be caused by invasion or compression of sensory nerves, distant from the site of irritation, and not by a local cutaneous lesion A detailed study of the distribution of pruritus in a case of Hodgkin's disease associated with a syndrome of cord and root compression, was made by Boudin *et al* (39) The pruritus did not *involve areas of dissociated anesthesia with suppression of heat,* cold and pain but no impairment of tactile sensation It was concluded that the afferent pathways conducting the sensation of pruritus follow the same route as those conducting heat, cold and pain They believed pruritus should be regarded as a sensitivity disturbance of the cerebrospinal system and not of the sympathetic system, and that it is received and conducted by the same elements and the same radiculo medullary routes as thermal and pain stimuli

Various therapeutic measures have been suggested to alleviate the pruritus of Hodgkin's disease Among these are roentgenotherapy, Grenz rays, ultraviolet light, hyperpyrexia, auto hemotherapy, chemotherapy and topical medications

Adequate irradiation of active primary lesions, as well as lymph nodes, spleen and skin, is of utmost importance, according to Craver (73a) For patients exhibiting no localized lesions, or when the process is so generalized that local irradiation is not practical, he advocated prolonged low intensity roentgen rays to a large portion, or even the entire body, to relieve the pruritus as well as other symptoms of Hodgkin's disease It is a well known fact that roentgenotherapy to enlarged lymph nodes results in disappearance of generalized pruritus and surgical removal of the principal area involved

may relieve pruritus even though the disease is present in other areas of the body

Grenz rays (soft roentgen rays) were found to be more effective than ultraviolet light (Bluefarb 36a) for the relief of pruritus However such treatment is not always available and generalized irradiation is difficult with this mode of therapy although it is of distinct benefit for localized pruritus

Ultraviolet light given in suberythema doses to the point of tanning without erythema is also of value for generalized pruritus These rays like roentgen rays appear to elevate the sensory threshold of the intraepithelial nerve endings Craver (73a) found this therapy gave some relief in cases of Hodgkin's disease and Rothman (281a) mentioned it for the relief of pruritus associated with lymphomas internal malignancy and pregnancy

Autohemotherapy has been found to be effective in relieving generalized pruritus in Hodgkin's disease and inoperable abdominal malignancy according to Sulzberger and Wolf (317b) This treatment consists of the withdrawal of 10 to 20 cc of blood from the antecubital vein which is immediately injected deeply into the buttocks The procedure may be repeated every two to four days A patient who had generalized pruritus for two years before lymphadenopathy appeared was described by MacCormac (207a) The pruritus became very slight following autohemotherapy and disappeared after the third injection

Hyperpyrexia in the form of short wave radiotherm hot cabinets hot baths and intravenous injections of triple typhoid vaccine have also been reported to be of benefit

Nitrogen mustard has been used in the treatment of pruritus of Hodgkin's disease Pruritus was a distressing symptom in four cases described by Wintrobe and Huguley (347) In two it was relieved when the general condition of the patient improved and disappeared in the terminal stages of the disease in the other two They found that neither the general condition of the patient nor the pruritus had been benefitted by nitrogen mustard therapy Urethane which has a central seda

tive effect was used with some success *in relieving the pruritus* of Hodgkin's disease according to Wolfram (353).

Arsenic therapy was advocated by Rook (277) for the control of pruritus. Fowler's solution in gradually increasing doses is given, although asiatic pills ($^1/_{16}$ gr. twice daily) may be administered for longer periods without evidence of cutaneous pigmentation or keratoses such as result from large amounts of Fowler's solution.

Rottino (282a) reported good results in nine patients having pruritus associated with Hodgkin's disease who were treated with sodium salt of adenosine 5 monophosphate with 20 mg/cc. of water injected hourly for five consecutive hours for three days. We were unable to confirm these results, and Rothman, Rostenberg and Becker (281d) were also of the opinion that adenylic acid is of no value in relieving this pruritus.

Because many of these patients have a dry skin (see Chapter V, No. 12, page 278), defatting agents should not be used. A calamine liniment is preferable to calamine lotion since the lotion is very drying, especially to a dry or ichthyotic skin. Various antipruritics, such as phenol, methol, liquor carbonis detergens or chloral hydrate, may be incorporated in the liniment. Bathing with soap and water, *unless the skin is oily, should not* be more frequent than once a week. The water should be tepid and the skin patted dry rather than rubbed, after which an emollient should be used.

When the pruritus is associated with jaundice caused by pressure of enlarged lymph nodes at the portal outlet, a reduction in the size of these nodes with roentgenotherapy may offer relief.

Herpes zoster (see Chapter V, no. 13, page 282), which *occurs in a fairly* large percentage of patients with Hodgkin's disease, may be preceded or accompanied by localized pruritus. It may be relieved by roentgenotherapy to the affected area, sodium iodide (1 gm.) injected intravenously every second day for four injections, or with flexible collodion painted on the involved area. Another occasional cause of localized pruritus according to Craver (73a) is involvement of a particular sector

of nerve roots or trunks and the pruritus may be a forerunner or aftermath of pain In such a case treatment consists of roentgen ray irradiation of the affected segment of the nervous system

3 Prurigo like Papules The synonyms for this cutaneous eruption are prurigo lymphadenique (Dubreuilh) prurigo lymphatica (Buschke) and lymphogranuloma pruriginosum (Kreibich) The most characteristic of the toxic cutaneous lesions in Hodgkin's disease is the scattered papule prurigo like papule When associated with intense pruritus and pigmentation the possibility of Hodgkin's disease even in the absence of lymphadenopathy should always be suspected A toxic papular eruption may occur not only in Hodgkin's disease but according to Arndt (9c) similar eruptions may be present in association with tuberculosis of the lymph nodes malaria and leukemia

Of the toxic cutaneous eruptions associated with Hodgkin's disease the prurigo like exanthema are second only to pruritus in frequency Cole (64a) reported this type of eruption in 18 per cent of 33 cases The papules are numerous "pinhead" to "split pea" size round or conical in shape firm to the touch pink to rose in color edematous and pruritic with a deep seated vesicle on the summit which is scratched off and replaced by a crust Occasionally these papular lesions have a true bright red urticarial inflammatory halo but they may be *semi translucent* yellowish red and waxy in appearance They are scattered over the trunk and extremities without predilection for the extensor surfaces and frequently have a *follicular* arrangement Wise (349) stated that the flexor surfaces are the more characteristic sites as opposed to the predominance of lesions on the extensor surfaces *in true* prurigo The prurigo like papules occur in crops and the pruritus increases with each new crop The distribution may become *generalized but the* papules are usually not found *on the* palms soles or genitalia Because of the intense pruritus the skin between the papules shows many scratch marks edematous lesions *pigmentation* thickening and lichenification The cutaneous surface eventu

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ally becomes dry and scaly and erythematous patches of irregu-
lar shape and size, or secondary pyogenic infections such a
impetigo and furuncles may occur

These eruptions, like pruritus, appear irregularly and afte
being present for several months, frequently disappear spon
taneously, or disappear from one site only to reappear in
another They may precede any visible lymphadenopathy





10 Prurigo like papules of the back (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

11 Prurigo like papules of the back

occur simultaneously with the lymphadenopathy, or appear late in the course of the disease The eruption may temporarily or permanently disappear just as the lymphadenopathy may show spontaneous or therapeutic involution as, for example, following roentgenotherapy The efflorescences have a marked resemblance to lichen urticatus

This type of cutaneous eruption was first described by Gowers (128) in 1879 but Dubreuilh (87) was the first to emphasize its presence in Hodgkin's disease More than 100 cases of this toxic manifestation were collected from the literature up to 1925 by Shelmire (298) A 36 year old man with intensely pruritic papular lesions preceding lymphadenopathy

was described by Janeway (162) The lesions were symmetrical on the forearms but spread rapidly to involve the entire body Three weeks later, left cervical lymphadenopathy occurred and was followed by lymphadenopathy on the right side Meanwhile, the cutaneous lesions had become generalized, sparing only the palms, soles and genitalia, and the papular eruption was most marked on the face, hands, scalp, chest, back and legs, with a tendency to grouping The papules were covered with a blood crust and the skin was excoriated There was also a diffuse generalized pigmentation of the skin and definite thickening of the skin on the dorsum of the hands had been present since the onset of the disease

The principal cutaneous lesions in two men, aged 44 and 63 years, respectively, were described by Raynaud *et al* (270) Both had pruriginous papules and diffuse lichenification as well as secondary pyogenic infection chiefly on the hands, feet and, in one patient, on the scalp Sabetta (286) reported a 64 year old woman with an erythematous papular eruption involving the arms, shoulders, chest, hips and thighs Michelson (220a) also described a 31 year old woman and a 56 year old man (220b) who had prurigo Parkes-Weber and Dove (251c) reported a 34 year old man who had a pruriginous eruption on the trunk and thighs consisting of numerous papules the majority of a reddish color and some resembling acne

MacLeod (208b) believed papular eruptions to be of inflammatory origin and due to the same cause as pruritus, not secondarily produced by scratching or rubbing However, Rolleston (275a) stated that prurigo-like papules are caused by scratching as a result of the pruritus Although scratching may cause papular eruptions, present opinion favors MacLeod's theory of toxic origin Wolf (352) on the other hand, believed this type of eruption often follows roentgenotherapy and there is a destruction of lymphocytes with liberation of foreign proteins The plausibility of this theory may be questioned however since many patients having this type of eruption did not receive roentgenotherapy We have observed

cases in which the eruption cleared following roentgenotherapy to the lymph nodes

The pathologic picture in this type of eruption is not specific but shows only an inflammatory reaction consisting of small round cell infiltrations around the sweat glands and no histological evidence of a lymphadenomatous growth. The epidermis is thickened and occasional formation of vesicles and chronic inflammatory changes of the superficial layers of the dermis occur. It should be borne in mind that papular cutaneous lesions may show a histological picture of Hodgkin's disease and are true Hodgkin's disease of the skin as discussed under that heading

The superficial ulcerated papules with secondary excoriations closely simulate scabies for which they are often mistaken. This difficulty in diagnosis is illustrated in a number of cases. A diagnosis of scabies was originally made in the case reported by Wright (355 case 7) of a 15 year old girl whose first symptom was pruritus. A 21 year old man reported by Shelmire (298 case 1) had loss of weight superficial lymphadenopathy and pruritus. He was treated for scabies for three weeks before the correct diagnosis was made. The cutaneous eruption in this case resembled scabies except that the burrows and typical localization of scabies were not present. A 34 year old patient described by MacLeod (208a) complained of spasmodic pruritus and the initial impression was that the patient had scabies. However subsequent lymphadenopathy established the true diagnosis. King Smith *et al* (171) reported a 30 year old woman who had a generalized pruritic papular scabies like eruption of 15 months duration. The case described by Parkes Weber and Dove (251c) was also regarded to be scabies at the onset of the illness

Case Report A 50 year old man first developed vesicular papular cutaneous lesions on the wrists buttocks abdomen and penis. Clinically the eruption resembled scabies and he was treated with sulfur ointment with no improvement. Subsequently he developed patches of pruritic eczematous dermatitis on the nape of the neck ears and face most marked on the

eyelids A hemogram at that time revealed 85 per cent hemoglobin 4 710 000 red blood cells and 16 300 white blood cells per cu mm with 25 per cent polymorphonuclears 69 per cent lymphocytes 2 per cent monocytes and 4 per cent degenerated forms A cervical lymph node then became palpable and histological examination revealed Hodgkin's disease

Prurigo like papules may simulate papulo-necrotic tuberculid An interesting feature of Rulison's (283b) case was the scarring suggestive of a papulonecrotic tuberculid on the arms and legs Crops of lesions varying in size and appearance either macular papular or indolent pustules lasting four to six weeks had been present for two years Some of the larger infiltrated lesions were ulcerated and remained discrete while the pruritus remained constant A woman described by White (342) had pigmentation and extensive excoriations with intense pruritus which strongly simulated pediculosis corporis

The prurigo like manifestations have no distinctive features according to Arndt (9c) and cannot be differentiated from prurigo like eruptions which occur in other diseases of the lymphatic system such as hyperplasia or granulomas associated with lymphosarcoma various forms of lymph node tuberculosis leukemia and prurigo like eruptions present in malaria Neither the clinical or histological pictures suffice to separate *this* type of prurigo from the others The papules must be distinguished from nodular cutaneous growths which are seldom associated with pruritus The traumatized papules healed lesions pigmented macules and scratch marks with occasional grouping are suggestive of dermatitis herpetiformis The scars of the healed papular lesions resemble papulonecrotic tuberculid (Rulison 283b)

A patient having unusual manifestations was described by Czczowska and Mierzecki (75) The generalized prurigo papules soon ulcerated and the individual lesions disappeared in a few days without treatment leaving a brown patch while new lesions appeared in successive crops An atypical case reported by Baum (19) presented hard nodules larger than a cherry in size partly annular but more often oval shaped

cases in which the eruption cleared following roentgenotherapy to the lymph nodes

The pathologic picture in this type of eruption is not specific but shows only an inflammatory reaction consisting of small round cell infiltrations around the sweat glands and no histological evidence of a lymphadenomatous growth The epidermis is thickened and occasional formation of vesicles and chronic inflammatory changes of the superficial layers of the dermis occur It should be borne in mind that papular cutaneous lesions may show a histological picture of Hodgkin s disease and are true Hodgkin s disease of the skin as discussed under that heading

The superficial ulcerated papules with secondary excoriations closely simulate scabies for which they are often mistaken This difficulty in diagnosis is illustrated in a number of cases A diagnosis of scabies was originally made in the case reported by Wright (355 case 7) of a 15 year old girl whose first symptom was pruritus A 21 year old man reported by Shelmire (298 case 1) had loss of weight superficial lymphadenopathy and pruritus He was treated for scabies for three weeks before the correct diagnosis was made The cutaneous eruption in this case resembled scabies except that the burrows and typical localization of scabies were not present A 34 year old patient described by MacLeod (208a) complained of spasmodic pruritus and the initial impression was that the patient had scabies However subsequent lymphadenopathy established the true diagnosis King Smith *et al* (171) reported a 30 year old woman who had a generalized pruritic papular scabies like eruption of 15 months duration The case described by Parkes Weber and Dove (251c) was also regarded to be scabies at the onset of the illness

Case Report A 50 year old man first developed vesicular papular cutaneous lesions on the wrists buttocks abdomen and penis Clinically the eruption resembled scabies and he was treated with sulfur ointment with no improvement Subsequently he developed patches of pruritic eczematous dermatitis on the nape of the neck ears and face most marked on the

Various theories regarding the causation of this pigmentation include generalized pruritus associated with scratching, involvement of the adrenal cortex by lymphogranulomatous tissue, irritation of the abdominal sympathetic nerves, as a result of therapy (arsenic, roentgen rays), avitaminoses and malnutrition and pressure by enlarged nodes on the adrenal veins with resulting adrenal insufficiency.

Generalized pruritus, with associated scratching, may result in pigmented macules and papules from excoriations, since



12 Prurigo like papules with excoriation (case report)
13 Increased pigmentation with prurigo-like papules and left cervical lymphadenopathy (Bluefarb and Schwartz *Arch Dermat*, Feb 1956)

pigmentation is often the direct result of continuous scratching and is analogous to cutaneous bronzing seen in patients with pediculosis corporis and dermatitis herpetiformis Brain (41) reported the occurrence of pigmented macules in areas where papules had either involuted or had become scratched A case in which the pruritus was so intense that hyperpigmentation and lichenification resembling neurodermatitis resulted, was described by Abramowitz (1b) Pigmentation associated with scratching was present in two cases described by Cole (64a cases 1 and 2) Ginsburg (121a case 2) reported a woman

over the thorax and upper arms. Some nodules were light red and other yellowish to brown in color with fine telangiectases and a silvery scale. The nodules broke down leaving necrotic scars. Baum stated that there was one case report in the literature describing localized necrotic areas such as occurred in his case. Pruritus with swelling of the follicle resembling cutis anserina was noted by Kren (178b).

A patient having a prurigo like papular cutaneous eruption of the lower extremities was presented by Webster and Bluefarb (335b). This 61 year old man had a generalized lymphadenopathy of one year's duration and mild pruritus which had occurred simultaneously with the lymphadenopathy. There was marked subjective improvement following roentgenotherapy but three months later the lymphadenopathy recurred and the pruritus became more severe. There was a bilateral symmetrical papular cutaneous eruption involving mainly the upper and lower extremities. Some of these well defined papular lesions were crusted and others excoriated. Hemogram revealed 62 per cent hemoglobin, 3,980,000 red blood cells and 16,500 white blood cells per cu mm with 58 per cent polymorphonuclears, 27 per cent band forms, 2 per cent lymphocytes and 13 per cent monocytes.

4 *Pigmentation.* Cutaneous pigmentation associated with Hodgkin's disease occurs in one of two forms. The most frequent is an increase of melanin pigment (melanoderma), the other an icteroid tint to the skin resulting from jaundice.

Increase of melanin pigment occurs in 10 to 30 per cent of the cases of Hodgkin's disease and is about five times more frequent than in leukemia. Pigmentation was present in 10 per cent of Epstein and MacEachern's (94) series of 156 cases, and Busman and Johnston (53) also found pigmentation in 10 *per cent of their series. Cole (64a) noted diffuse pigmentation* in 30 per cent of 13 cases of Hodgkin's disease. A good average is probably about 20 per cent. A striking degree of melanin type pigmentation in a patient having the clinical picture of lymphoma would therefore be suggestive but not diagnostic of Hodgkin's disease according to Jeghers (163).

Various theories regarding the causation of this pigmentation include generalized pruritus associated with scratching, involvement of the adrenal cortex by lymphogranulomatous tissue, irritation of the abdominal sympathetic nerves, as a result of therapy (arsenic, roentgen rays), avitaminoses and malnutrition, and pressure by enlarged nodes on the adrenal veins with resulting adrenal insufficiency.

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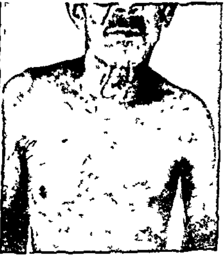
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who had *intense pruritus, most marked at night,* affecting various parts of the body The skin was darkly pigmented but a visible eruption could only be produced by vigorous scratching A 37 year old woman who had a brownish pigmentation of the face and hands, associated with intense pruritus, was described by Falconer and Leonard (98) A *man with a striking* bronzing of the skin, accompanied by intense pruritus, was mentioned by Graham-Little (129)

When involvement of the adrenal cortex by lymphogranulomatous tissue occurs, there is a deep pigmentation resembling





14 Increased pigmentation resembling pediculosis corporis (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

15 Increased pigmentation resembling Addison's disease

Addison's disease present particularly on the abdomen Minot and Isaacs (227) were of the opinion that this pigmentation is due to impairment of *the adrenal capsules and in their series* of cases, abnormal pigmentation developed in 5 per cent of 401 patients who had received arsenotherapy A 33 year old *woman who had generalized* pigmentation resembling Addison's disease was described by Molfino (229) The pigmentation was most marked in areas of friction from clothing around

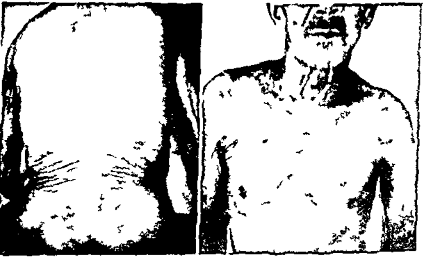
scar tissue and in the areola of the nipples Autopsy revealed the sclerosing type of generalized Hodgkin's disease and the adrenals appeared somewhat atrophic Histologically, there was increase in the connective tissue stroma and compression of cell cords in the cortex The vessel walls were thickened and there was occasional grouping of lymphocytes while the medulla was reduced to slender strands of small cells Morquio (232) reported marked melanoderma which he believed could be explained by the presence of extensive granulomas in the adrenal glands as revealed at autopsy Pigmentation associated with masses of lymphogranulomatous tissue about the adrenal glands has been described by Bramwell (42) Fowler (105) La Porte (185) Nieskowski (244) and Symmers (320)

Pigmentation due to irritation of the abdominal sympathetic nerves has been described Although Bramwell's (42) patient had not received arsenic the pigmentation was like that of Addison's disease and was explained as due to irritation of the sympathetic nerves since autopsy revealed the abdominal aorta to be surrounded by enlarged nodes Irritation of the sympathetic nerves by lymphogranulomatous nodes surrounding the solar plexus was reported by Fowler (105) The cutaneous lesions in Symmers (320) patient a 35 year old man were described as acanthosis nigricans and the coeliac plexus was invaded by lymphadenomatous nodes but the adrenals were not affected Chloasma like spots on the extremities and trunk or pale brown pigmentation about contact areas of the body (axillae groins and other areas) and even intense widespread bronzing of the skin is not infrequent, irrespective of pruritus ingestion of arsenic or roentgenotherapy Shelmire (298) believed that some cases could be explained as being due to involvement of the solar plexus with lymphogranulomatous nodules as in Jenner's (164) case Rolleston (275b) also was of the opinion that pigmentation results from irritation of the sympathetic nerves rather than from adrenal involvement

Pigmentation resulting from roentgen ray or arsenic therapy has been reported The patient reported by Bowen (40) was

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marily involved and there may be only a deepened color about the eyelids, axillae, nipples, pubes and genitalia. The skin folds become accentuated at times and very often resemble acanthosis nigricans. In such cases the sites of irritation are prone to pigmentation. Another group exhibits brownish pigmentation in irregular areas about the chest and abdomen giving the skin a piebald appearance. A third group presents generalized, evenly distributed pigmentation resulting in gradual darkening of the skin.

The pigmentation of Hodgkin's disease may be extremely bizzare. A young man described by Wile (343b), was treated for exfoliative dermatitis with topical medication and improved rapidly. However, less than a month later a band of deep brown pigmentation appeared around the waist extending to the upper thighs together with hyperpigmentation of the axillae. There was sufficient cutaneous thickening to suggest acanthosis nigricans. This patient also had marked inguinal and axillary lymphadenopathy.

The pigmentary cutaneous changes must be differentiated from pigmentation secondary to various dermatoses such as lichen planus, dermatitis herpetiformis, scleroderma, Addison's disease and lipomelanotic reticulosis.

Oral pigmentation is rare. Minot and Isaacs (227) noted the buccal mucosa was less frequently involved than the skin of the face, back of the hand, trunk, axillary or genital regions. When oral pigmentation is present it is usually due to ingestion of arsenic.

Jaundice may be produced by compression of the large biliary ducts and more frequently from infiltration of the liver by lymphomatous lesions. It may occur in the Pel-Ebstein syndrome in association with febrile bouts and superficial lymphadenopathy but recede with subsidence of the fever and lymphadenopathy. Other causes of jaundice associated with Hodgkin's disease are viral hepatitis and hemolytic anemia. The skin presents a peculiar icteroid or greyish tint in cases associated with fever according to MacNalty (209). The jaundice is of the obstructive type when compression of the

a 36 year old white woman whose skin color was that of a Negress She had a generalized pigmentation, except for the palms and soles This bronzing was not uniform and the deeper color in some areas resulted in a mottled appearance However, Shelmire (298) believed this patient had lymphosarcoma rather than Hodgkin's disease Arsenical pigmentation, due to ingestion of pentavalent and inorganic arsenic preparations such as Sol potassium arsenite (Fowler's solution) N F IX, sodium cacodylate, and arsenic trioxide, is a rather characteristic generalized pigmentation presenting a "rain drop" appearance in the depigmented areas Arsenic may cause pigmentation of the buccal mucosa in some cases and keratoses of the palms and soles associated with the pigmentation has also been noted

Pigmentation due to avitaminoses and malnutrition is similar to that found in pellagroid states No demonstrable cause for the pigmentary changes could be found in some cases Pigmentation varying from yellowish brown over the face, blackish brown over the enlarged axillary lymph nodes, to a black color about the nates was reported by Lehndorff (187) Autopsy revealed lymphogranulomatosis of the internal organs although the adrenals and solar plexus were not involved by the process Pellagroid dermatitis occurs more frequently on exposed parts of the body such as the dorsa of the hands, face neck occasionally the forearms, and usually on the mucous membranes Less common sites are the elbows, knees, shoulders scrotum and perineum A ring of hyperpigmentation around the neck (Casal's collar) is characteristic of pellagra The condition is manifested first by erythema, then fissuring and finally by a dry sharply defined dermatitis with a predilection for the hair follicles of the dorsa of the hands Pigmentation becomes prominent following subsidence of the dermatitis

Pigmentation from pressure on the adrenal veins by enlarged nodes resulting in adrenal insufficiency is similar to that found in involvement of the adrenal cortex by lymphogranulomatous tissue In some cases the normal pigmented regions are pri

studied and on this basis it would appear to be at most an infrequent cause

2) Patients with jaundice showing liver involvement by Hodgkin's granuloma demonstrated diffuse involvement of the portal trinities with fibrotic Hodgkin's disease

3) Non jaundiced patients with liver involvement by Hodgkin's granuloma did not show this complex

4) In patients with liver involvement with Hodgkin's sarcoma the etiology of the jaundice is not clear but intervening liver necrosis in the cases with jaundice was demonstrated while it was absent in the non jaundiced patients

5) Patients developing jaundice immediately prior to death may show no histologic evidence of liver disease

5 **Bullous and Vesicular Lesions** These lesions are rare in Hodgkin's disease and when present are usually a terminal manifestation of the disease These lesions should not be confused with the bullous type of erythema multiforme which may occur in Hodgkin's disease Vesicular eruptions usually occur with intense pruritus occasionally during elevations of temperature appear gradually and recur frequently The vesicles are of various sizes some tense others flaccid and appear on diffusely reddened or less frequently on normal skin Frequently the clinical picture of the skin and mucous membranes resembles pemphigus The eruptions have *often* been ascribed to external causes such as trauma pressure of cloth [illegible]

in [illegible]

les [illegible] Hodgkin's disease His patient a 60 *year old man* had widespread Hodgkin's disease of the lymphatic nodes and internal organs and a recurrent pruritic pemphigus like cutaneous eruption consisting of vesicles and bullae scattered over the body A bullous form of erythema multiforme was described by B Bloch (31) in a 52 year old woman who had *recurrent* palm sized " erythematous plaques over the entire body Vesicles and bullae *from* 0 5 to 2 5 cms in *size* developed over these erythematous areas and appeared in the

biliary duct system occurs The frequency of jaundice in Hodgkin's disease is about 4 to 6 per cent Lesser clinical jaundice and plasma jaundice is present in more than 10 per cent of all cases, according to Minot and Isaacs (227) An incidence of 6 per cent, in a total of 220 cases, was reported by Jackson and Parker (159d)

A 22 year old Negro who presented jaundice as the initial symptom of Hodgkin's disease was reported by Pepper (256) Burke and Hamid (51) described severe jaundice due to obstruction of the neck of the gallbladder by enlarged lymph nodes Autopsy proved the case to be Hodgkin's disease Low grade jaundice associated with pruritus and bronzing of the skin, appearing four years before Hodgkin's disease, was reported by Talbott (321 case 5) Other cases of Hodgkins disease associated with jaundice have been mentioned by MacLeod (208b), Symmers (320) Craver (73c), L B Goldman and Victor (124b) and Reimann *et al* (271)

When associated with obstruction of the biliary duct jaundice will disappear following irradiation of the affected area The jaundice often fluctuates in severity and may disappear spontaneously, or with radiation therapy, but recurs at varying intervals

Ahrens *et al* (5) treated two patients with primary biliary cirrhosis and intrahepatic blockage of bile flow, using methyl testosterone Lloyd Thomas and Sherlock (196) reported the use of methyl testosterone in the treatment of chronic pruritus in seven patients having obstructive jaundice

Jaundice is not rare in Hodgkin's disease, according to Beatty (20) who found the average incidence reported in the literature to be from 3 to 8 per cent His studies were conducted to either confirm or dispute the prevailing opinion that jaundice is usually due to obstruction by compression or obliteration of the extrahepatic biliary ducts by Hodgkin's disease His conclusions were as follows

1) Obstruction of the extrahepatic biliary ducts played no demonstrable part in the production of jaundice in the cases

studied and, on this basis it would appear to be at most, an infrequent cause

2) Patients with jaundice showing liver involvement by Hodgkin's granuloma demonstrated diffuse involvement of the portal trinities with fibrotic Hodgkin's disease

3) Non jaundiced patients with liver involvement by Hodgkin's granuloma did not show this complex

4) In patients with liver involvement with Hodgkin's sarcoma the etiology of the jaundice is not clear, but intervening liver necrosis in the cases with jaundice was demonstrated while it was absent in the non jaundiced patients

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Yamasaki (358) first reported the association of bullous lesions and Hodgkin's disease His patient a 60 year old man, had widespread Hodgkin's disease of the lymphatic nodes and internal organs and a recurrent, pruritic, pemphigus like, cutaneous eruption consisting of vesicles and bullae scattered over the body A bullous form of erythema multiforme was described by B Bloch (34) in a 52 year old woman who had recurrent "palm sized" erythematous plaques over the entire body Vesicles and bullae, from 0 5 to 2 5 cms in size, developed over these erythematous areas and appeared in the





16 Lesions of bullous erythema multiforme in a terminal stage (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

17 Severe pyoderma (hidradenitis suppurativa in a patient with Hodgkin's disease) (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

mouth from time to time Histologic examination of granulomatous tissue from diseased lymph nodes and deposits in internal organs showed a classical picture of Hodgkin's disease, while the cutaneous lesions showed banal vesicle formation with perivascular round cell infiltration of the terminal vesicles of the papillary bodies and a slight increase in the connective tissue cells of the stroma

Konigstein (176) described a 43 year old man who had an eruption which closely resembled pemphigus vulgaris There were sharply circumscribed patches of vesicles in annular or arc like arrangement on the extensor surfaces of the extremities and vesicles and bullae of the same arrangement occurred in the mouth The histologic findings were identical with those reported by B Bloch (34), namely, true lymphogranulomatous tissue in the lymph nodes and internal organs and banal inflammation in the cutaneous lesions

A patient who had both a specific and nonspecific or toxic, cutaneous eruption, was described by Hoffmann (153) There were serous or hemorrhagic bullae, 0 5 to 3 0 cms in size, scattered over the neck arms fingers, chest and back which were usually present on normal skin but occasionally had an erythematous zone Nodules, 0 5 to 1 5 cms in size, and a bluish infiltration appeared on the neck concomitant to the bullae formation Since the bullae tended to develop *at the sites* of trauma, such as the hands Hoffmann considered the eruption to resemble epidermolysis bullosa hereditaria. Histologic examination of lymph nodes and cutaneous tumors, however, revealed Hodgkin's disease while *the* vesicular and bullous lesions were not specific The bullous lesions disappeared with irradiation to the enlarged lymph nodes but *recurred* with the reappearance of lymphadenopathy

Similar cases, having granulomatous cutaneous *nodules* in association with bullous eruptions were noted by Corbett (68) Sibley (300a) and in a case presentation (57a) H E Freeman (108b) described a 62 year old man who had recurrent crops of vesicles on the face and scalp recurrent pustules on the forearms and erythema of the face for seven months

Madden's (210a) patient, a 26 year old man had vesicular and papular cutaneous lesions on the flanks and flexor surfaces of the extremities A patient who had multiple bullae was reported by L B Goldman (124a) In a 62 year old man Boge (37) noted frequent recurring hemorrhagic bullae of the hands and lower legs associated with an intensely pruritic eczema Singh (302) reported a 51 year old Chinese man who complained of periodic pruritus of the legs with vesicle formation and oozing for a period of two years There was an associated blood eosinophilia of 50 per cent Talbott's (321 case 4) patient had a bullous erythema multiforme preceding Hodgkin's disease

A 53 year old man who had Hodgkin's disease complicated by an unusual type of erythema multiforme following blood transfusion was described by Costello (71) He had first developed cervical lymphadenopathy which was believed to be due to infectious mononucleosis There was a blood eosinophilia and anemia Three years after the appearance of lymphadenopathy, he developed a cutaneous eruption which appeared three days after a blood transfusion At that time the hemogram revealed 3,400 000 red blood cells and 2 700 white blood cells per cu mm Sternal bone marrow examination revealed granular hyperplasia, especially of the eosinophils and erythroblastic hyperplasia The cutaneous lesions consisted of irregularly shaped early lesions having a central crust surrounded by greyish black coalescing bullae, *which in turn were surrounded by an area of pink erythema* and small discrete vesicles in corymbiform arrangement guttate, tense shotty bullae surrounded by a thin halo of erythema and short lived crusted lesions on the face which suggested generalized herpes simplex Sjogren (304) described an 82 *year old man whose predominant symptoms were cutaneous* lesions of a bullous type resembling erythema multiforme

6 ***Urticaria*** Urticarial eruptions are frequently present in Hodgkin's disease and are usually transitory and evanescent in character, merely representing a toxic manifestation of the disease Urticaria has been described by MacNalty (209)

Cole (64a case 11) and by Kreibich (177) in whose case the generalized urticaria preceded other symptoms of the disease by six months I B Goldman (124a) noted urticaria in three of 212 cases We have observed urticaria in a 54 year old woman in whom the urticarial wheals and pruritus were the first manifestation of Hodgkin s disease Richter (273) described a patient with cutaneous lesions presenting the clinical picture of urticaria papulosa Busman and Johnston (53) reported three cases of urticaria associated with Hodgkin s disease In one patient the severe urticaria disappeared following roentgenotherapy to a mass of inguinal lymph nodes but recurred six months later when new nodes became palpable Jaffe (161a) reported a 26 year old man in whom urticaria was the predominating symptom Falconer and Leonard (98 case 6) described a patient with urticaria associated with Hodgkin s disease of the lung Although urticaria is frequently mentioned in the literature as a toxic manifestation of Hodgkin s disease dermographism is seldom mentioned and some believe dermographism is never associated with urticaria due to Hodgkin s disease.

Schoenhof (293) stated that diffuse urticaria as it was formerly seen is infrequent He mentioned a 65 year old man who had typical generalized lymphadenopathy who developed an unusually dense large macular urticarial erythema on the trunk and extremities a few weeks before death A second patient had an urticarial eruption present from the onset of the disease which disappeared after roentgenotherapy to the involved lymph nodes However two years later urticaria of the chest and back and scaly lesions resembling pityriasis rosea recurred in association with generalized lymphadenopathy A 27 year old woman who had urticaria with multiple excoriations was described by Mallory (212b) However prior to the development of the urticaria she had received penicillin The erythematous macular toxic eruptions are more frequent in Hodgkin s disease than in leukemia Morbilliform eruptions were described by L T Webster (336) and by Barron (18) in whose case an eruption simulating German measles recurred

several times after a diagnosis of Hodgkin's disease had been established

The cutaneous eruption in a 17 year old boy, reported by Skeer (306), consisted of numerous erythematous patches of irregular size and shape Rulison (283a) described a woman who had a bluish red erythema which occurred in irregular patches and merged with normal skin without a definite border, involving both cheeks, temples, portions of both ears, and the postaural area Macular eruptions were also noted by Cole (64a case 12) in one patient

A scarlatiniform eruption was described by Klein (174) and a pale, erythematous eruption about the eyelids was noted by Reimann *et al* (271) Rosacea-like and large nodular exanthemata were reported by Heissen (143) and by Fullenbaum (112) Cerutti's (58 case 2) patient was a 51 year old man whose cutaneous lesions began as large round macules of pink or reddish color on the trunk and extremities Erythema multiforme was reported by Andrews (8a) in a six year old boy who had received roentgenotherapy to the cervical lymph nodes An intense, generalized pruritus developed four months later and subsequently a generalized erythematous cutaneous eruption with circinate and gyrate lesions appeared on the buttocks, thighs and arms Erythema multiforme with Hodgkin's disease was also reported by Arzt (10d) and Fuller (113)

In the differential diagnosis of these erythematous toxic lesions allergic phenomena, pyogenic infections, tuberculosis and the exanthematous stage of leprosy must be considered

7. *Pyoderma* Furunculosis may be a toxic manifestation of Hodgkin's disease but more frequently it is secondary to the pruritus and due to secondary infections Impetigo, ecthyma, abscesses, lymphangitis and lymphadenopathy, secondary to *the scratching, are also not infrequent findings*

Primary furunculosis was described by Senear and Wien (294d) and by Gordon (126) L B Goldman (124a) noted furunculosis in three of 212 cases in his series

A 45 year old Negro who had cellulitis of the scalp associated with Hodgkin's disease was presented by J R Webster and

Bluefarb (335a) He had developed lymphadenopathy and pruritus 14 months previously and was given nitrogen mustard therapy However, intractable pruritus developed four months after treatment Six months later he developed a "pimple" on the left side of the face followed by swelling of the face, neck and scalp on the same side The scalp became soft and there was a purulent discharge and crusting There was a papulo



18 Diffuse cellulitis of the scalp (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

pustular eruption on the left side of the face and the left occipito-parietal area of the scalp Hemogram revealed 63 per cent hemoglobin 3 610 000 red blood cells and 8 650 white blood cells per cu mm with 56 per cent polymorphonuclears 16 per cent band forms 16 per cent lymphocytes and 12 per cent monocytes

8. Edema. Edema is a sign observed in advanced Hodgkin's disease It is usually related to lymph stasis or vascular obstruction by enlarged lymph nodes The areas most frequently involved are the genitalia, portions of the face, or one or more extremities Minot and Isaacs (227) found that edema of one or both legs was occasionally a late symptom, but rarely the initial symptom of the disease In their cases, the edema could be attributed to obstruction of blood and lymphatic flow by pressure of masses of lymphomatous tissue and distinct lymphadenopathy, usually present in the groin or lower abdomen, when the edema developed

Edema was mentioned as an outstanding symptom by Reimann *et al* (271) and Cole (64a) noted edema in three cases Subcutaneous edema was reported by Ambler (7) and Jaffe's (161a) patient had edema of the legs and genitalia Elephantiasic edema of the penis and scrotum was described by Sanchez-Covisa and de la Cuesta (288) and the patient reported by Pasztay (255) had edema of the hands and feet

The first symptom of the 20 year old man reported by Symmers (320 case 3) was ankle edema Autopsy revealed compression of the iliac veins by enlarged lymph nodes resulting in edema of the lower extremities

9. Exfoliative Dermatitis. The first signs of Hodgkin's disease may be an exfoliative dermatitis or generalized erythroderma which, in many instances, have proved to be nonspecific However, Montgomery (230) stated that histopathologic study usually permits a definite differentiation between exfoliative dermatitis caused by any one of the various benign dermatoses, and those of lymphomatous etiology

Diffuse exfoliative erythroderma in Hodgkin's disease was first reported by Wechselmann (337) However, Shelmire (298) believed this case to be "aleukemic" leukemia rather than Hodgkin's disease and he questioned most of the reported cases of true universal exfoliative dermatitis or erythroderma associated with Hodgkin's disease He stated that most investigators believed Nicolau's (243) case of exfoliative dermatitis associated with Hodgkin's disease to be "aleukemic" leu-

kemia and Bosellini's (38) case corresponded more closely to the tuberculous form of generalized erythroderma (erythrodermia exfoliativa universalis tuberculosa) described by Brunsgaard (481). In Bosellini's case true tubercle formation was found in the erythematous and exfoliating skin and many tubercle bacilli were demonstrated with Ziehl-Neelsen staining.



19 Exfoliative dermatitis associated with Hodgkin's disease (Bluefarb and Schwartz, *Arch Dermat*, Feb 1956)

However there are reports of true exfoliative dermatitis associated with Hodgkin's disease. Loveman (203) described a [illegible]

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les[illegible] showed a definite nonspecific lymphogranulomatous infiltrate whereas the lymph node histology was specific for

8 *Edema* Edema is a sign observed in advanced Hodgkin's disease It is usually related to lymph stasis or vascular obstruction by enlarged lymph nodes The areas most frequently involved are the genitalia portions of the face or one or more extremities Minot and Isaacs (227) found that edema of one or both legs was occasionally a late symptom but rarely the initial symptom of the disease In their cases the edema could be attributed to obstruction of blood and lymphatic flow by pressure of masses of lymphomatous tissue and distinct lymphadenopathy, usually present in the groin or lower abdomen when the edema developed

Edema was mentioned as an outstanding symptom by Reimann *et al* (271) and Cole (64a) noted edema in three cases Subcutaneous edema was reported by Ambler (7) and Jaffe's (161a) patient had edema of the legs and genitalia Elephantiasic edema of the penis and scrotum was described by Sanchez Covisa and de la Cuesta (288) and the patient reported by Pasztay (255) had edema of the hands and feet

The first symptom of the 20 year old man reported by Symmers (320 case 3) was ankle edema Autopsy revealed compression of the iliac veins by enlarged lymph nodes resulting in edema of the lower extremities

9 *Exfoliative Dermatitis* The first signs of Hodgkin's disease may be an exfoliative dermatitis or generalized erythroderma which in many instances have proved to be nonspecific However Montgomery (230) stated that histopathologic study usually permits a definite differentiation between exfoliative dermatitis caused by any one of the various benign dermatoses and those of lymphomatous etiology

Diffuse exfoliative erythroderma in Hodgkin's disease was first reported by Wechselmann (337) However Shelmire (298) believed this case to be aleukemic leukemia rather than Hodgkin's disease and he questioned most of the reported cases of true universal exfoliative dermatitis or erythroderma associated with Hodgkin's disease He stated that most investigators believed Nicolau's (243) case of exfoliative dermatitis associated with Hodgkin's disease to be "aleukemic leu

kemia and Bosellini's (38) case corresponded more closely to the tuberculous form of generalized erythroderma (erythrodermia exfoliativa universalis tuberculosa) described by Brunsgaard (481) In Bosellini's case true tubercle formation was found in the erythematous and exfoliating skin and many tubercle bacilli were demonstrated with Ziehl Neelsen staining



19 Exfoliative dermatitis associated with Hodgkin's disease (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

However there are reports of true exfoliative dermatitis associated with Hodgkin's disease Loveman (203) described a 50 year old man who had a generalized exfoliative dermatitis palpable liver generalized lymphadenopathy weight loss fever and subcutaneous nodules Histologically the cutaneous lesions showed a definite nonspecific lymphogranulomatous infiltrate whereas the lymph node histology was specific for

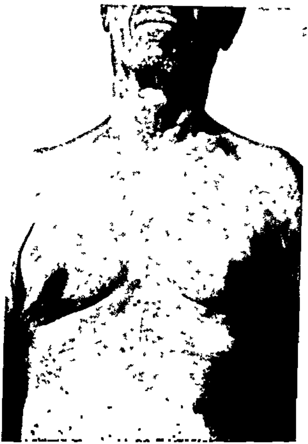


20 Homme Rouge type of erythroderma associated with Hodgkin's disease

Hodgkin's disease Symmers (320) reported two cases one a 20 year old man and the other a 12 year old girl who had jaundice as well as exfoliative dermatitis Bruck (47) reported a 17 year old boy with extensive erythroderma "walnut sized cutaneous tumors and striae atrophicae Marianis (214) patient a 42 year old man had a desquamative erythematous process first localized on the hands and feet and later becoming generalized to involve even the head with a diffuse redness and giving the skin a pasty quality Lortat Jacob and Solente (200) also described erythroderma associated with Hodgkin's disease

Jones and Alden (166) reported generalized Hodgkin's disease in a Negro boy who had a generalized intensely pruritic cutaneous eruption lymphadenopathy and ultimately loss of hair These symptoms in a young person showed a clinical similarity to pityriasis rubra of Hebra The cutaneous lesions were for the most part papules varying from "pinhead" to "pea" size the tops of which were weeping and scaling There were scratched and excoriated areas and a few soft but firm "walnut" sized nodules on the arms legs and sides of the abdomen The ears face and scalp were involved in an eczematous process which produced a leonine facies

Although nonspecific generalized erythrodermas are not uncommon in Hodgkin's disease a universal specific granulomatous infiltration is rare as was present in Miller's (224a case 1) case This 62 year old patient had generalized pruritus followed by an infiltration of the entire cutaneous surface including the scalp palms and soles which preceded the lymphadenopathy by four months This patient presented a nonspecific pre lymphogranulomatous eruption followed by a specific or granulomatous one The eruption was probably nonspecific at first because of its transient character but later as the disease progressed became very extensive fixed in character and had the histologic picture of Hodgkin's disease Miller's (224a case 2) second patient a 34 year old man had edema of the face trunk and extremities The entire cutaneous surface had been reddened and extremly pruritic for three and one half years There were deep fissures over most flexures with many raised wavy infiltrated plaques scattered over the body most marked on the trunk The infiltrations covered about one third of the cutaneous surface and those on the temples scalp and neck were of "hen's egg" size while many areas on the back showed ulceration and secondary infection The fine branlike scales generalized lymphadenopathy loss of hair and nails and ulceration over pressure points suggested pityriasis rubra of Hebra During the few weeks preceding death the edema subsided and the skin particularly that of the extremities became atrophic *The diagnosis of*



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athy of two to three months duration and pruritus most marked at night of 12 months duration Pigmentation most marked on the trunk had been present for one month and there was a red scaly dermatitis on the legs while the skin of the face was highly colored One year later the patient developed "homme rouge" with a sort of universal exfoliative dermatitis A similar case was reported by Porter (263) two cases by Burnam (52) and two cases by L B Goldman (124a)

The erythroderma is characterized by subacute or chronic progressive reddening which spreads gradually over a large part of the cutaneous surface Flaky or bran like scales are formed and either regional or more commonly generalized lymphadenopathy occurs The skin may become thickened and edematous or may be atrophic and thinned Subjective sensations of chilliness may be marked due to increased loss of heat and pruritus may be a prominent feature (Bluefarb 36d) Arndt (9a) stated that the histological changes are in a continuous diffuse or more circumscribed infiltration of the upper layers of the dermis where the blood vessels are greatly dilated The infiltration is formed by small deeply staining round cells which are morphologically identical to small lymphocytes and by larger elements with pale oval nuclei interpreted as proliferative connective tissue cells which are diffusely spread whereas the lymphocytes surround hair follicles sweat and sebaceous glands In addition mast cells and pigment cells the latter sometimes numerous may be present The rete Malpighi is mostly atrophic and covered by a more or less hypertrophic horny layer Burnam (52) believed that this type of cutaneous manifestation of Hodgkin's disease is not amenable to treatment

Loveman (203) described a 55 year old man who developed cutaneous lesions as the first manifestation of Hodgkin's disease One year previously he had used a "rust remover" and the penis and scrotum had become contaminated from the presence of this product on his hands The following day his hands wrists and scrotum were pruritic reddened and inflamed and this dermatitis gradually spread to involve the entire body with an extremely pruritic exfoliative dermatitis There was consider

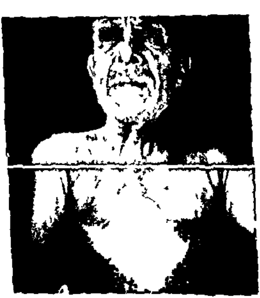
Hodgkin's disease was made only after histologic examination at autopsy. This case presented a generalized nonspecific eruption which preceded the development of lymphogranulomatous nodules by three and one-half years

Similar cases were reported by Arndt (9a), Dossekker (84) and by Breitkopf (43) who observed an intensely pruritic eczematoid eruption of the entire body consisting of small, "eruptive," red papules which finally resulted in a "leather-like" thickening of the entire skin Zieler (363a,b) observed a patient with a nearly universal scaly erythroderma of vaguely limited pale redness and desquamation Mulzer and Keining (234) reported vesicle formation resulting in universal erythroderma in a patient who had intense pruritus The primary *lesions were single but eventually the entire body became a* vivid red and was covered with a whitish-grey scale, sparing only the face and scalp There were numerous petechial hemorrhages and flacid, *tense* are hemorrhagic vesicles were numerous on the extremities, while isolated superficial erosions, apparently the result of previously ruptured vesicles, were present in the sacral region

Exfoliative dermatitis has also been described by Lamb and Stout (181), Hoffmann (153), Saalfeld (285), Frei (110), Arzt (10b), Wile and Belote (343c) Haxthausen (139), Cole and Driver (64b) O'Leary *et al* (247a) Schaumann (289), MacLeod (208b), Richter (273) Gross (131), Milian (223a), Dahmen (76), Lohe (198), Favre (100a), Gottron (127) and Schmidt (292) *They all designated exfoliative dermatitis* as the primary eruption While the eruption apparently preceded other signs and symptoms of the disease, lymph node involvement may have been merely imperceptible or inaccessible, at the time The diagnosis of Hodgkin's disease should always be considered when generalized erythroderma, even without perceptible lymphadenopathy is present

Mumford (235) described an unusual type of generalized erythroderma with pin point concretions in the skin which broke down and flaked off, leaving small white scars Parkes-Weber and Dove (251c) *commented on the case of a* 35 year old man who had cervical, axillary and inguinal lymphadenop-

A case resembling localized neurodermatitis was reported by Abramowitz (1b) This patient was a 47 year old man who had a generalized pruritic eruption and whose skin appeared hyperpigmented and lichenified with numerous crusted excoriations Guszmann (134) also described a case of lichen simplex chronicus L B Goldman (124a) reported eczematous lesions on the upper extremities and Craver (73a) com



21 Exfoliative dermatitis (case report) (face view)
22 Exfoliative dermatitis (case report) (chest view)

mented that these lesions respond promptly and permanently to small doses of unfiltered or very lightly filtered low voltage roentgen rays

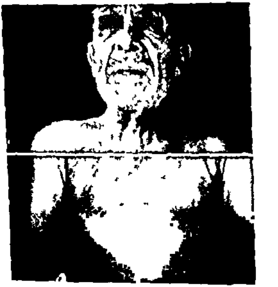
Frasers (107a) patient a 65 year old man had pruritus followed by an eczematous eruption of round or oval red and scaling lesions with well defined borders 1 to 3 by 5 cms in size involving the back chest and tibial surfaces In Busman and Johnstons (53) series of 30 cases five patients presented

able loss of hair of the scalp eyebrows axillary and pubic regions He had a generalized lymphadenopathy with "lemon" sized moderately firm lymph nodes in the axillae The liver was palpable and the knee jerks diminished In some areas the skin was thickened and lichenified and there was marked hyperkeratosis of the palms and soles He had lost considerable weight and the body temperature was elevated The histologic picture of the cutaneous lesions revealed a nonspecific type of lymphoma and the lymph node histology was characteristic of Hodgkin s disease

Case Report A 54 year old man first developed a small granular elevated moderately pruritic cutaneous eruption on the right ankle two years previously A similar erythematous vesicular eruption then appeared over the entire dorsum of this foot and subsequently involved the left foot and both legs By the following year the eruption had become generalized Severe pruritus caused scratching which resulted in a thickened nodular skin This thickened verrucous skin was most marked on the dorsal aspect of the feet and the skin of the forearms was infiltrated There was moderate cervical and inguinal lymphadenopathy and marked axillary lymphadenopathy Five months later he presented a marked generalized erythema with definite thickening and scaling of the skin in several areas The intense pruritus had continued He responded poorly to roentgenotherapy which relieved the pruritus for only a short time Histologic examination of a lymph node revealed an increase in fibrous tissue and reticulum cells numerous eosinophils and occasional Sternberg Reed cells Examination of the skin disclosed reticulum cells and considerable infiltration of eosinophils He died two and one half years after onset of the illness and the autopsy diagnosis was cutaneous Hodgkin s disease

10 Eczematoid and Psoriasiform Lesions Localized eczematoid patches sometimes occur in Hodgkin s disease Ill defined lesions may be a prodromal symptom and should be distinguished from contact or atopic dermatitis according to Montgomery (230) This is also true for psoriasis and parapsoriasis

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maculopapular lesions Richter (273) cited Dittrich (82) and Geipel and Linser (117) as having described patients who had more or less diffuse eczema

Van der Meiren's (330 case 2) 76 year old patient had chronic lichenified eczema of the left arm and another (330 case 3), a 20 year old man, had a generalized pruritic eczema like eruption which was resistant to all treatment Miescher (222) presented a 73 year old man with parapsoriasis en plaques The histological picture, at that time, suggested mycosis fungoides but two years later lesions typical of Hodgkin's disease developed He died one year later and autopsy revealed Hodgkin's disease of the inguinal, periaortic, iliac and mesenteric lymph nodes

11. Erythema Nodosum. Hodgkin's disease must be added to the ever growing list of etiological factors of erythema nodosum Fuller (113) described a 44 year old woman who had *erythema nodosum for two months before the appearance* of cervical lymphadenopathy which, on histological examination, revealed Hodgkin's disease Cases of erythema nodosum have also been described by Fraser (107a) and Taylor (322)

12. Trophic Changes. Trophic changes, including dryness of the skin, atrophy, hyperkeratosis of the palms and soles, alopecia and nail changes, are frequently present in Hodgkin's disease

Dryness of the skin with superficial desquamation, is a common finding and L B Goldman (124a) noted its occurrence in 20 of 212 cases Ayres Jr (12) reported generalized dryness with slight thickening and roughening of the skin in a 68 year old woman whose forearms and legs had a marked "pebble-like appearance Madden (210a) noted marked dryness of the skin of a 26 year old man This type of trophic change may, at times progress to atrophy

The onset of ichthyosis vulgaris in an adult with no personal or family history of this disease is unusual The simultaneous occurrence of Hodgkin s disease and ichthyosis therefore, should arouse suspicion of a cause and effect relationship Ronchese (276) described such a case of ichthyosiform atrophy with

hyperkeratosis in a 24 year old man who had Hodgkin's disease which resulted in death 11 months later Widespread changes occurred during the six weeks preceding death and the cutaneous surface was covered by rhomboidal scales with flaky edges of the type seen in mild or senile icthyosis Histological examination revealed atrophy and hyperkeratosis of the skin but no evidence of the infiltration found in Hodgkin's disease Similar changes were present in Glazebrook and Tomaszewski's (122) patient who also had severe impairment of the liver and marked disturbance of vitamin A metabolism They suggested that this type of generalized icthyosiform atrophy of the skin might have been secondary to the vitamin A disturbance Recent studies by Brown *et al* (46) have indicated the integrity of the reticuloendothelial system as an important factor in vitamin A metabolism

J R Webster and Bluefarb (335c) presented a 22 year old Negro who had icthyosis associated with Hodgkin's disease He first developed a small "knot" in the left axilla 11 months previously which gradually enlarged to the size of a small grapefruit" and became painful He had lost 23 pounds in weight and dryness of the skin had begun at the time the lymphadenopathy appeared There was occasional mild pruritus of the arms and slight scaling of the lower extremities as well as a moderate follicular keratosis The liver and spleen were palpable The lymphadenopathy decreased slightly following triethylene melamine therapy Hemogram revealed 31 per cent hemoglobin 1 790 000 red blood cells and 5 400 white blood cells per cu mm with 56 per cent polymorphonuclears 22 per cent band forms 1 per cent eosinophils 19 per cent lymphocytes and 2 per cent monocytes

Another case of icthyosis associated with Hodgkin's disease was presented by Bluefarb and Goldberg (36e) This patient a 58 year old woman had cervical axillary and inguinal lymphadenopathy for five years before the development of fever night sweats fatigue and anorexia She had received intensive roentgenotherapy and nitrogen mustard therapy during this period The skin became red and scaly one year after

the lymphadenopathy appeared and had slowly increased in severity. The skin, particularly that of the face and extremities, appeared erythematous with a generalized superficial exfoliation There was hyperkeratosis of the palms and soles and the hair of the scalp was sparse and coarse while the eyebrow and axillary hair was absent There were a few palpable inguinal lymph nodes, the heart was enlarged to the left and there was a systolic murmur at the apex Hemogram revealed 34 per cent hemoglobin, 2,120,000 red blood cells and 9,750 white blood cells per cu mm with 69 per cent polymorphonuclears, 22 per cent band forms, 6 per cent lymphocytes and 3 per cent monocytes

Welch and Epstein (340) reported a 55 year old man with acquired icthyosis in whom histologic examination of a lymph node disclosed Hodgkin's disease A case of acquired icthyosis associated with Hodgkin's disease was also described by Sneddon (311) Andrews' (8c) patient with Hodgkin's disease had icthyosis and keratodermas, and Bruck's (47) patient had associated atrophicae striae Numerous cases of atrophy limited to the skin of the extremities have been reported The patient mentioned by Chargin (61) developed macular atrophic areas secondary to the development of cutaneous nodules and infiltration Lamb and Stout (181 case 3) described a 43 year old man who had generalized dryness of the skin resembling icthyosis McGlasson and Lehmann's (206 case 2) patient, a 30 year old woman, had a very dry, rough, thickened skin early in the course of Hodgkin's disease which involved most of the body but was most marked on the legs and dorsa of the feet and felt like sandpaper to the touch

A case of primary cutaneous Hodgkin's disease in a patient who had an icthyotic skin was reported by Fairburn (97) In the discussion of this case, Hellier (144) stated it 'might well belong to the group of cases of Hodgkin's disease which start in an icthyotic form,' and described a boy who had lesions on the abdomen which he believed were due to infection and, therefore, made a diagnosis of xeroderma However, the

lesions progressed gradually and four to five years later Hodgkin's disease was apparent

Hyperkeratosis (thickening of the palms and soles) resembling keratoderma may develop Marked thickening or exfoliation of both palms and soles is not an uncommon occurrence, as reported by Loveman (203) and by Jones and Alden (166) whose patient was an 18 year old Negro boy In describing such a case Sweitzer (319a) stated that marked thickening or exfoliation of both the palms and soles is not uncommon in any of the lymphomas and is frequently misdiagnosed as keratoderma or some type of eczema Nanta and Chatellier (239c) also noted icthyosiform hyperkeratoses in their patient

Alopecia may involve the scalp and eyebrows and patchy alopecia of the scalp may occur Cases reported by Fox (106) and Cole (64a) were associated with alopecia areata Cannons (56a) patient a 20 year old girl had numerous toxic lesions including pruritus dryness prurigo like papules and pigmentation of the skin There was alopecia of the outer margin of the eyebrows total absence of suprapubic and axillary hair and partial baldness of the occipital region The cutaneous symptoms were present for two and one half years before the appearance of lymphadenopathy The character of the hair may be altered and become dry in texture and change in color as in Bramwell's (42) case where the hair became lighter finer and softer Jones and Alden (166) described patchy alopecia which progressed until no body hair remained except a soft down like growth on the scalp Hair loss associated with pruritus has been reported by Parkes Weber and Dove (251c) Nanta and Baudru (239b) and Colrat (66) and may be due to inflammation around the hair follicles as a result of prurigo and pruritus However Porter (263) described a patient who had nearly universal loss of hair but did not mention the presence of pruritus There may be merely a thinning of the hair but no alopecia as pointed out by Shelmire (298) Complete alopecia was noted by Busman and Johnston (53) in one patient who also had a flexural dermatitis The diagnosis was made on histological examination of a single

small discrete right infraclavicular lymph node There was prompt regrowth of hair and disappearance of the cutaneous *lesions following roentgenotherapy*

The occurrence of dystrophic nail changes have frequently been reported Miller (224i) stated that the nails may become thickened and appear "moth eaten and he reported the eventual loss of all nails in his patient In Cannons (56i) patient the nails were thin and short with some scaling striation grooving and marked atrophy The patient described by Glazebrook and Tomaszewski (122) had smooth polished finger nails which showed alternating light and dark areas resulting in a curious striped appearance This striation did not involve the toe nails A patient having total onycholysis with paronychia associated with Hodgkins disease was described by Arzt (10c)

Lloyd (195) described a 33 year old man who had clubbing of the fingers and toes as well as periosteal thickening of the radius and ulna This is a rare case with hypertrophic osteoarthropathy secondary to Hodgkins disease of the mediastinal lymph nodes

Hyperhidrosis is not uncommon in Hodgkins disease and is probably due to disturbance of the heat regulating mechanism

13 Herpes Zoster Herpes zoster is more frequently present in Hodgkins disease and lymphosarcoma (4 to 7 per cent) than in lymphocytic leukemia (1 per cent) Although there are few reports of herpes zoster associated with Hodgkins disease undoubtedly many cases are observed and not recorded since this association is not rare and occurs more frequently than is generally recognized

According to Warner (334) herpes zoster occurs at some time during the course of Hodgkins disease in approximately *30 per cent of all cases However this figure appears high* when compared with the findings of other observers Craver and Haagensen (73e) noted zoster in three of 59 cases of lymphosarcoma and in three of 72 cases of Hodgkins disease In a study of 445 patients having lymphomatous diseases Epstein and MacEachern (94) found zoster to be most fre

quent in Hodgkin s disease occurring in 2 5 per cent of these patients L B Goldman and Victor (124b) noted zoster in 24 of 319 cases of Hodgkin s disease an incidence of 7 5 per cent while Jackson and Parker (159d) found an incidence of 4 per cent in 220 cases Sturgis (315) stated that zoster occurs in about 2 5 per cent of all cases while Surkes (318) found zoster in four of five patients with Hodgkin s disease Beek (22) compared the incidence of zoster in association with other cutaneous manifestations and found zoster occurred in 48 per cent of the patients having Hodgkin s granuloma in 32 per cent having varicella like eruptions and in 4 per cent with prurigo like papules The zoster was of the gangrenous type in 58 per cent of these cases

In Hodgkin s disease the specific virus of zoster is stimulated by the compression of the granuloma along the ganglion or nerve In a discussion of the complications of new growths within the chest J N Hall (137) stated that zoster occasionally occurs along the nerve compressed by a new growth Zoster may be caused by any tumor and is frequently observed in patients having metastatic carcinoma and lymphomas

The following theories as possible factors in the causation of zoster are listed by Pancoast and Pendergrass (250) 1) Irritation of nerves by toxins (Mitchell *et al* 228) in 1864 demonstrated that irritation and not section of a nerve was the cause of zoster) 2) Compression by tumors and 3) Prolonged neuritis this supposes that zoster is simply the result of an inflammatory irritation transmitted by continuity of tissue from a nerve twig or branch to the cutaneous elements among which it is distributed

The essential differences are noted in a comparison of zoster occurring in Hodgkin s disease and in leukemia Invasion of the ganglion by leukemic cells which acting as a "trigger factor stimulate the specific virus of zoster and is usually the causative factor in leukemia whereas in Hodgkin s disease the zoster is usually caused by compression of the ganglion or nerve by the Hodgkin s granuloma according to Pancoast and Pendergrass (250) They found the average age in which

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found foci of leukemic infiltrations in the dura, epidural tissues, cranial nerves, spinal roots and gasserian ganglion. The gasserian ganglion was involved in four of nine cases in which it was studied, although none of these patients had herpes zoster despite known ganglion involvement. Similar negative evidence was reported by Kirch (172) who described cases of neurofibromatosis with one or more spinal ganglia tumors not associated with herpes zoster.

Six cases of herpes zoster associated with Hodgkin's disease were described by Baldridge and Awe (15). One patient developed zoster over the distribution of the fourth right thoracic nerve and three months later collapse of the body of the fourth dorsal vertebra due to a metastatic lesion occurred. The zoster appeared shortly before death in another patient and autopsy study of the dorsal root ganglions and vertebra showed no gross metastases. Kobro's (175) patient was a 20 year old man who had superficial lymphadenopathy of the cervical, axillary, inguinal and mediastinal regions. Histologic examination of the lymph nodes revealed Hodgkin's disease. Destructive processes in the sixth and twelfth thoracic vertebrae and in the fourth and fifth lumbar vertebrae were followed by involvement of the ninth and tenth thoracic vertebrae. Seven months later herpes zoster appeared in the area corresponding to the ninth and tenth thoracic cutaneous segments. Kobro concluded that the possibility of a columnar disease in patients with zoster must be considered, although a nonspecific lesion of the spinal ganglia would not appear sufficient to provoke zoster and would seem only to prepare the field for the specific zoster virus.

Pancoast and Pendergrass (250, case 1) described a 27 year old woman who developed zoster late in the course of Hodgkin's disease and a 49 year old woman (250, case 4) who developed zoster early in the disease. They believed that an irritation caused by a mass of glandular enlargements in close proximity to the spinal ganglion caused the herpes zoster. Goldman and Victor (124b) noted that zoster usually indicated perineural extension in their cases. One patient had this lesion

zoster occurred with leukemia to be the fifth decade, while zoster was more frequent in the second decade when associated with Hodgkin's disease Zoster was much more frequent in men than in women with leukemia while it affected men only slightly more often in Hodgkin's disease Herpes zoster generalisatus was much more frequent in leukemia, occurring in more than 50 per cent of the cases, and may be attributable to the lowered resistance of the older age group Herpes zoster can be severe in both diseases but there appeared to be more tendency toward ulceration, scarring keloid formation and sloughing in Hodgkin's disease Paralytic manifestations appear to be more frequent in leukemia, while bone involvement is much more common in Hodgkin's disease

All classic herpes zoster was regarded by Marinni (214) to be due to injury to the nervous system However, it would appear that this lesion could be caused by pressure on a nerve or its spinal ganglion, or by toxic products of diseased tissue The theory that spinal ganglion lesions cause herpes zoster was proved incorrect by Wohlwill's (351) comprehensive pathological studies of this disease when he examined the entire peripheral nervous system in six cases of idiopathic, and four cases of secondary zoster in patients who had gastric carcinoma, lymphosarcoma, lymphocytic leukemia and syphilis as the primary disease He found involvement of the spinal ganglia was not constant in either the idiopathic or secondary types of herpes zoster and in a case where the disease was due to carcinomatous infiltration of the anterior branch of an intercostal nerve the dorsal ganglia remained intact In another case there was involvement of the posterior root and in another the posterior horn of the spinal cord while the dorsal ganglion was not affected These findings led to the suggestion that herpes zoster may be produced by involvement of any point of the afferent portion of the reflex arc The dorsal ganglion however, remains the most frequent point of involvement

The pathogenesis of herpes zoster was further complicated by subsequent studies of the nervous system in 12 cases of leukemia by Tromner and Wohlwill (328) They frequently

zoster Ginsburg (121a case 6) reported a woman who developed herpes zoster and right facial paralysis as a terminal manifestation of Hodgkin's disease in addition to a complete spastic paraplegia with sphincteral involvement Craver and Haagensen's (73e case 1) patient had involvement of the segmental area of the ninth dorsal nerve which occurred simultaneously with splenomegaly and suggested to them the possibility of a correlation between the two symptoms Another patient (73e case 5) had zoster of the segmental areas of the second and third lumbar nerves coexisting with involvement of the iliac bone on the same side which they believed suggested extension of the disease to nearby structures

The severity of zoster associated with Hodgkin's disease is often emphasized since the hemorrhagic or gangrenous type is frequent and severe scarring often results Deep gangrenous sloughing ulceration has also been described A 40 year old woman reported by Madden (210b) was given roentgenotherapy to the axillary and cervical lymph nodes Three weeks later an extremely severe destructive gangrenous zoster appeared on the right side of the head with the slough extending to the outer table of the skull in some areas Comparatively little pain was associated with the eruption A deep crateriform ulcer the center covered with an adherent gangrenous slough was present on the right side of the neck and scalp Extending anteriorly on the forehead and neck were several "olive sized" ulcers of irregular shape having polycyclic borders and clean granulation tissue bases Ginsberg (121a case 7) described a 34 year old woman who developed a profuse herpetic eruption first involving the third to fifth dorsal nerve segments and later becoming generalized and sim lat ne

...area of the fifth dorsal nerve This eruption formed an irregular oblong edematous vesicular red patch 15 to 20 cms posteriorly and anteriorly along the fifth to seventh dorsal nerves Ten days later numerous diffuse discrete vesicles containing clear fluid appeared

involving the ophthalmic branch of the trigeminal nerve and a similar involvement of the sixth right dorsal segment appeared five months later There was also deep upper cervical lymphadenopathy Involvement of two nerve segments was also described by Lockwood *et al* (197) Herpes zoster thoracalis appeared in B Bloch s (34) patient following healing of the first bullous eruption and true diffuse herpetic lesions were noted by Boge (37) in two cases

A patient described by Middleton (221 case 7) was a 40 year old man who developed zoster on the flexor aspect of the right forearm Areas of vesiculation appeared along the cutaneous nerves derived from the eight cervical and first second and third thoracic posterior roots Burnam (52) reported two cases of zoster which was limited to the neck in both patients Lisa (194b) described a 63 year old woman in whom Hodgkin s disease was preceded by zoster of the left side of the chin arm and chest which healed without scarring Left axillary lymphadenopathy developed and about four months later weakness and weight loss occurred A symmetrical dry gangrene of the toes fingers elbows and ears appeared ten months after the onset of zoster and was diagnosed as Raynaud s disease Histologic examination of a lymph node revealed Hodgkin s disease Downing s (85) patient was a 73 year old woman in whom zoster was followed by red scaly patches on the neck hips thighs and legs which finally became generalized

Jackson and Parker (159f) described a 35 year old man with painless lymphadenopathy involving the left side of the neck which showed typical Hodgkin s granuloma on histological study He was given roentgenotherapy Five years later he suddenly developed weakness and numbness of both legs which became completely paralyzed within a few days He was then given high voltage roentgenotherapy over the dorsal spine and one month before the last treatment he developed a broad band of herpes zoster corresponding to the distribution of the fourth right thoracic spinal nerve This eruption cleared within three weeks leaving a broad scar resulting from the

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(213) was a 37 year old man who developed zoster in the right posterior axillary region the segmental area of the fifth dorsal nerve This eruption formed an irregular oblong edematous vesicular red patch 15 to 20 cms posteriorly and anteriorly along the fifth to seventh dorsal nerves Ten days later numerous diffuse discrete vesicles containing clear fluid appeared

over the entire trunk, face and scalp with a few on the thighs and spread to involve the entire lower extremities within 24 hours. This vesicular eruption continued to spread until the entire body was affected and the vesicles became pustular before drying up, thus simulating smallpox. However, the history did not indicate this disease; there had been a successful vaccination and the vesicular pustules were not painful. Marcellus believed this case to represent the simultaneous occurrence of Hodgkin's disease, herpes zoster and varicella. It is known that herpes zoster tends to become generalized when associated with the lymphomas and this case is therefore probably Hodgkin's disease associated with herpes zoster generalisatus.

Miller (224a) described a patient with Hodgkin's disease who became almost moribund but recovered following a severe gangrenous zoster. A 57 year old Negro who had a pruritic eruption for three years before he developed an extremely painful zoster of the right side of the face and neck which became ulcerated was reported by H. Freeman (108a). Parkes Weber (251a) also described a similar case and L. P. Barker (17) reported generalized herpes zoster in a patient with Hodgkin's disease. Severe scarring following zoster was present in the patients described by Sibley (300b) and Andrews (8b).

Case Report. A 38 year old man first developed weakness and weight loss two years before admission to the hospital. Three months after the appearance of these symptoms he developed a severely pruritic generalized cutaneous eruption which responded to local therapy within a few days. Two months later he developed pain in the upper right side of the abdomen. The hemogram revealed 38,000 white blood cells per cu. mm. with 86 per cent polymorphonuclears. At this time there was no evidence of cutaneous involvement but six weeks later he had developed a vesicular eruption on the right lower chest which extended from the spine to the mid chest anteriorly. This severe herpes zoster consisted of grouped ulcerated lesions surrounded by a red areola. He died

eleven days after the appearance of the zoster and the autopsy diagnosis was generalized Hodgkin's disease

Case Report A 34 year old man first developed mild cervical lymphadenopathy, weight loss and general malaise nine years previously Despite deep roentgenotherapy, he had repeated exacerbations of the disease Four years after the onset he developed osseous erosion of the second lumbar vertebra and right sacroiliac joint which responded to roentgenotherapy Four years later he had marked weakness of the lower extremities and definite hyperasthesia beneath the level of the fifth dorsal dermatome bilaterally Surgical examination disclosed a large extradural tumor in the region of the second third and fourth dorsal vertebrae but the entire mass could not be removed Four months after surgery he developed typical cutaneous lesions of herpes zoster involving the right shoulder and upper arm Several days later a diffuse generalized cutaneous eruption appeared and the lesions tended to ulcerate and form scab encrusted areas 2 to 3 mms in diameter He died nine days after the appearance of the herpes zoster and the diagnosis of Hodgkin's disease was confirmed at autopsy

Case Report This 31 year old man had Hodgkin's disease of four years duration for which he had received roentgenotherapy since the onset of the illness He then developed a few small "blisters" having an erythematous border on the right side of the chest several days after a course of irradiation *These* [illegible]

[illegible] sensation There was an extremely painful diffuse pin point sized vesicular eruption surrounded by an erythematous flare which was typical of herpes zoster During the following six months he was given further roentgenotherapy However six months after the last treatment he developed a continuous dull ache accompanied by severe sharp pain in the right side and hip On exertion a shooting pain appeared from the groin to the lateral aspect of the hip and down to just below the knee There had been progressive swelling of the right thigh concomitant with the pain Histo-



23. Herpes zoster involving right side of chest and right arm (case report)

logic examination of the lymph nodes at autopsy disclosed an almost complete replacement of their normal architecture and a few follicles remaining There was a marked pleomorphism of the cells with numerous eosinophils and Sternberg Reed cells in the majority of the sections as well as marked fibrosis and many giant cells Other sections showed hyalinization Multinucleated giant cells which appeared to be Langhan s giant cells were also present

It is believed that zoster may result from arsenical therapy However arsenicals are rarely used in present day treatment and zoster continues to be a common occurrence Cases have been reported however which were definitely attributed to arsenotherapy The patient described by Parkes Weber (251a) was an eight year old boy who had been given arsenical therapy for Hodgkin s disease He developed a typical zoster on the right chest and a generalized vesicular eruption on the trunk Andrews (8b) reported a 29 year old man who had been treated with roentgen rays and arsenic previous to the development of severe gangrenous zoster of the left supra orbital region The zoster cleared leaving marked scarring, but the neuralgic pain continued Zoster of the left side associated with mediastinal lymphadenopathy following the ingestion of Liq potassium arsenite in doses of ten drops three times daily was reported by Lloyd (195) Sibley s (300b) patient was a 16 year old boy who soon after ingestion of arsenic developed severe neuralgic pain over the left lower ribs A severe gangrenous zoster followed and resulted in deep scarring

Although these cases show a relationship between zoster and arsenical therapy there are reports of many more patients who did not receive arsenic However it may be concluded that the arsenic acts as a "trigger factor" in the development of zoster when administered prior to the appearance of herpes zoster

Many cases of herpes zoster associated with Hodgkin s disease have occurred in children Lamper (192) described a six year old boy who had herpes zoster as the presenting symp



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When the purpuric lesions occasionally show a specific, rather than a nonspecific infiltrate histologically, they are classed with the lymphogranulomatids

The association of purpura was noted by Cole (64a) in two of 33 patients with Hodgkin's disease One patient (64a case 3) was a four year old girl who had petechiae on the abdomen and scapula and another (64a case 9) had a generalized purpuric eruption In Parkes-Weber's (251b) patient who had recurrent purpura and hemorrhagic symptoms, the *condition* simulated chronic sepsis in the early stages The presence of splenomegaly, purpura and systolic murmur at the mitral valve made the exclusion of chronic malignant endocarditis (endocarditis maligna lenta) difficult This association of purpura and Hodgkin s disease was also reported by Desjardins and Ford (80b) and by Cade and Roubier (55) whose patient had intensely pruritic petechiae of the extremities Brain s (41) patient had dermal and subdermal nodules as well as purpura Diffuse erythroderma, bullae and blackish blue petechial hemorrhages appeared on the lower legs, buttocks and, to a lesser extent, on the elbows and flexor surfaces of the thighs in the patient described by Mulzer and Keining (234)

Jaffe (161a) described several cases of purpura associated with Hodgkin's disease One, a 27 year old man, had petechial hemorrhages of the chest, abdomen and forearms and numerous hemorrhages of the oral mucosa The subdural and intracerebral hemorrhages resulted in death A hemorrhagic diathesis is not common in Hodgkin's disease and usually occurs in the fulminating acute type which is often associated with severe anemia The possibility of a complicating septicemia must be considered in cases of Hodgkin s disease with a hemorrhagic diathesis

15. ***Rare Miscellaneous Toxic Lesions*****·** POIKILODERMA A case in which poikiloderma atrophicans vasculare eventuated in Hodgkin's disease was reported by Graham Little (129) The cutaneous features were universal bronzing, intense pruritus minute purpuric spots and telangiectasia, as well as hemorrhagic areas on the palate and pharynx *A patient with rapidly*

tom The zoster developed along the course of the left tenth intercostal nerve There were also four subcutaneous nodules on the anterior wall of the chest on the same side which, on histologic examination, revealed Hodgkin's disease A 17 year old boy, reported by Craver and Haagensen (73e case 4) had zoster on the same side as a large mediastinal tumor, suggesting a correlation between the two processes Among 11 cases of Hodgkin's disease in children, Charache (60) reported herpes zoster occurring late in the course of the disease in two patients An 11 year old boy who developed zoster following roentgenotherapy for Hodgkin's disease was described There were two children in the series reported by Pancoast and Pendergrass (250) The first (250 case 2) was a 10 year old girl who developed zoster early in the disease with keloids resulting from the zoster lesions and the other (250 case 3) was a 9 year old boy who developed zoster early in the disease Lockwood *et al* (197) reported a 15 year old boy whose first symptoms were bilateral herpes zoster, more pronounced on the left side, backache and weakness of the legs A roentgenogram revealed definite destruction of the bone in the first four lumbar vertebrae, ilium and femurs, although no definite changes had been noted in these structures six months before Histologic examination of an inguinal lymph node established the diagnosis of Hodgkin's disease The course of the disease was increasingly severe, with destruction of the bone of the dorsal and lumbar vertebrae, ilium and femurs and involvement of the lungs, liver, skeletal muscles and all lymph nodes Sibley's (300b) patient was a 15 year old boy and Parkes-Weber (251a) described an 8 year old boy with herpes zoster associated with Hodgkin's disease

14. **Purpura.** Although the occurrence of purpura has been observed in Hodgkin's disease it is more frequent in the leukemias Hemorrhagic tendencies were noted in 27 9 per cent of the leukemic patients as compared with 2 5 per cent in Hodgkin's disease, by Epstein and MacEachern (94) The hemorrhagic tendencies are usually a terminal manifestation in Hodgkin's disease but may be an initial symptom in leukemia



24 Phleb tis of the leg (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

B Specific Lesions

In 1906 Grosz (133) reported On a Hitherto Undescribed Disease of the Skin (Lymphogranulomatosis Cutis)" which was the first description of cutaneous lesions having the specific structure of Hodgkin s disease He described a 21 year old man who had lymph idenopathy most marked in the cervical and axillary regions and a "doughy" infiltration of the skin of the right side of the face arm and chest There were numerous brownish cutaneous tumors on the right side of the chest which were of "lentil to walnut size Although the small lesions were firm the larger ones were soft and finally ulcerated The

progressive cutaneous lesions of Hodgkin's disease was described by Lane (182) The first detectable growth was near an ulcer in an atrophic area of poikiloderma Poikiloderma is discussed more fully in the section on Mycosis Fungoides (Part I)

LICHEN PLANUS-LIKE ERUPTIONS A 41 year old man with *Hodgkin's disease who developed lichen planus was presented* by Weidman (338) He contended that lichen planus should be considered a toxic eruption, in this particular case

LICHEN NITIDUS Bechet (21) described a 25 year old man with Hodgkin's disease who had small, glistening slightly raised, noninflammatory papules on the backs of the hands, penis and neck There was a tendency toward aggregation in patches in the latter area Wise (349b) stated that the cutaneous lesions in this case resembled lichen nitidus and the coexistence of Hodgkin's disease indicated that the systemic and cutaneous manifestations were dependent upon the same etiological factors

WEBER-CHRISTIAN DISEASE A case resembling Weber-Christian disease in a 45 year old man was described by Reimann *et al* (271)

FROEHLICH SYNDROME D'Amore (78) reported a 30 year old man who had intractable pruritus for four months Examination revealed a typical Froehlich's syndrome and peripheral lymphadenopathy, while roentgenograms revealed deformity of the sella turcica and the anterior and posterior clinoid processes There was bilateral hemanopsia Histologic examination of a lymph node revealed Hodgkin's disease

SJOGREN'S SYNDROME Rothman *et al* (281c) reported Sjorgen's syndrome associated with Hodgkin's disease and hypersplenism, in a 49 year old woman

DERMATOMYOSITIS There have been an increasing number of reports of dermatomyositis associated with internal carcinoma Curtis, *et al* (74) described Hodgkin's disease associated with dermatomyositis

PHLEBITIS Recurring phlebitis may not only occur in association with carcinoma, especially pancreatic carcinoma, but has also been seen in association with Hodgkin's disease



24 Phlebitis of the leg (Bluefarb and Schwartz *Arch Dermat*, Feb 1956)

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histologic picture of the cutaneous lesions and the lymph nodes were the same both showed lymphogranulomatous tissue with Sternberg Reed cells

Although cutaneous Hodgkin s disease may develop in true



25 Phlebitis of the leg

skin many of the nonspecific lesions are merely extensions from neighboring lymph nodes or deep subcutaneous lesions As a rule specific cutaneous lesions are localized to the trunk and neck rarely on the extremities The head is seldom involved

in Hodgkin's disease whereas the lesions are usually localized on the face in leukemia

The specific cutaneous lesions occurring in Hodgkin's disease may be classified as 1) papules, 2) infiltrations or plaques, 3) nodules or tumors, 4) ulcerated lesions, 5) mixed or combinations of these, and 6) erythroderma Specic cutaneous lesions, associated with nonspecific or toxic lesions, may also be present

1. Papular Lesions The papular lesions appear as small, brownish red, flattened papules of a rather firm consistency Nobl (245b) described them as resembling syphilitic papules which may enlarge from 0 5 to 2 0 cms in size He described a 21 year old man who had superficial lymphadenopathy and brownish red papules on the chest which were "partly scattered and partly in groupings of more or less local infiltrations " In the case described by Bruusgaard (48b), the infiltration was formed by deep seated brownish red, flattened papules which were more diffuse in the periphery of the infiltration

The patient reported by Bersack (27c) had "hundreds" of small, circumscribed, papular erythematous lesions covering the body from "head to foot" associated with fever, severe chills and stupor These ulcerated papules resulted in a terminal spread through the blood stream A 21 year old man, described by Heuck (148), had superficial lymphadenopathy and "palm sized" groupings of four to seven rosy red, "lentil sized" papules in the right fossa ovalis The larger lesions were flattened and some had follicle like depressions in the center There was a slight leukocytosis of the peripheral blood This patient also had a diffuse lupus vulgaris Sweitzer and Winer (319b) reported a 47 year old man who first developed papules which disintegrated and eroded then enlarged and coalesced with no tendency to spontaneous healing Some of the smaller ulcers were covered with brownish crusts and had a granulating purulent base There were several nonulcerated papules interspersed between the ulcers Histological examination of the border of an ulcer revealed ulcerative Hodgkin's disease of the skin H E Freeman's (108a) patient had a generalized eruption of firm nodules and papules which was *most* marked

on the thighs and legs Histologic examination of a cutaneous papule and an inguinal lymph node showed Hodgkin's disease

The Negro patient, described by Brivey and Lamb (44), had an intense generalized pruritus and a dry, leathery, markedly thickened and scaly skin There were papular lesions over the forehead, upper chest and back In addition there was infiltration, lichenification and furrowing of the skin of the ears and face, giving a leonine appearance Histological examination of an inguinal lymph node disclosed that much of the architecture was obliterated by an increase of the connective tissue stroma Here and there, broad bands of partly hyalinized fibrous connective tissue were apparent and the number of sinus cells was increased There were minute focal areas of necrosis scattered throughout and numerous eosinophilic granulocytes were present in many areas Occasional large cells having an indented or double nuclei of the Sternberg-Reed type were observed He was given a total of 32 mg nitrogen mustard, intravenously, following which the pruritus became less intense, the lymphadenopathy diminished and the nodularity and thickening of the skin decreased

Rulison's (283a) patient was a 38 year old woman who developed an erythematomacular papular cutaneous eruption, without exfoliation, two months before the appearance of lymphadenopathy The white blood cells numbered 11,900 per cu mm and the skin and lymph node histology was typical of Hodgkin's disease A 68 year old man, described by Strandberg (314), had lichenified, brownish red papules on the back which were grouped symmetrical and follicular The lesions resembled lichenoid syphilis Later, the papules showed a central depression The eruption cleared following roentgenotherapy Histologic examination of a cutaneous lesion revealed Hodgkin's disease

Hovelborn (155) believed that the "abortive type" of Hodgkin's disease, without lymph node involvement, offers a relatively good prognosis and he mentioned four cases of this type One patient who had developed red inflammatory areas between cutaneous papules at four and one-half years of age

was observed for eight years These 2 cm lesions spread within six weeks to involve the arms legs face neck and scalp The patient appeared grotesque due to confluent raised brown to reddish granulations and thick scars which covered the face neck arms and legs There was extensive crust and scale formation on the scalp with a purulent secretion Histologic examination of a lesion from the arm disclosed "fully developed Hodgkin s disease

2 *Infiltrations or Plaques* The cutaneous infiltrations in Hodgkin s disease *when situated deeply are frequently discernible only on palpation* They are usually diffuse and appear to be most frequent in the breast

Neumann and Pick (240) reported a 37 year old woman who had cervical and axillary lymphadenopathy There was swelling of the left breast and lamellar tumors cutaneous nodules and globular tumors in the subcutis of the chest The skin was of a yellowish color and the process resembled an early "cancer en cuirasse" except for the absence of a distinct mammary tumor The peripheral blood showed a slight leukocytosis and histologic examination of the cutaneous tumors disclosed Hodgkin s disease granuloma gigantocellulare eosinophilicum (Pick) The patient described by Baker and Mann (14 case 5) was a 56 year old man who developed a plaque on the left breast The condition was diagnosed as carcinoma and mastectomy was performed but histologic *examination revealed* Hodgkin s disease

A 54 year old woman reported by Ginsburg (121b case 1) had pain in the right shoulder a "lump" *in the right* axilla progressive weakness and loss of weight for seven months There was an old 16 *cm* scar in the right breast which extended into the axilla The right breast was twice the *size of the left* and the skin was thickened and wrinkled and showed two punched out ulcerations The right arm was markedly edematous and there was a hemorrhagic infiltration over the chest There was a "plum sized" very firm homogeneous greyish colored cutaneous mass on the right breast which was "gristly" in texture and from which strands of similar tissue extended

"crab-like" through the adipose tissue and into the underlying tissue The pectoral muscles were almost completely absorbed and the fascia above the thorax was markedly infiltrated by this firm grey tissue There was invasion of the mass in one of the veins and its vasa vasorum The histologic structure of the lesion was typical of Hodgkin's disease

A man reported by Miller (224a) presented red, thickened, infiltrated, scaly skin of the face and entire body and thickened deep fissures on the hands and feet, including the palms and soles The eruption was markedly pruritic and "enormous amounts" of bran-like scales were shed on scratching This cutaneous eruption preceded the lymphadenopathy by four months The body was entirely devoid of hair, except for a few shafts on the scalp and bearded region, and the nails were markedly thickened and covered with longitudinal striae There was generalized superficial lymphadenopathy, the cervical nodes were of "pigeon egg" size, those in the axillae of "chicken egg" size and the inguinal nodes were the size of an "orange" All were firm, discrete and painless The mediastinal lymph nodes were only slightly enlarged *This patient* presented a nonspecific cutaneous eruption followed by a specific lesion

Primary cutaneous Hodgkin's disease in a 41 year old man was reported by Fairburn (97) This patient had icthyosis from infancy and an unchanging, mottled, brown pigmentation with vitiligo like patches had involved the trunk, neck and, to a lesser degree, the face and extremities Widespread, relapsing atopic eczema, with concomitant asthma, had been present since early childhood and although the eczema had subsided ten years previously the asthma had persisted There had been a relapsing alopecia of the scalp since the age of 20 years A cutaneous eruption consisting of small, dull red nodules had appeared on the anterior aspect of the thighs four years previously and had gradually spread to involve the trunk and, to a lesser extent, the extremities Slowly enlarging, painless dusky red, infiltrated plaques had appeared during the last 18 months which, on histologic examination showed dense dermal in

vasion of reticulum and lymphoid cells with occasional eosinophils and binucleate giant cells Widespread lymph node involvement had been evident for two months and a cervical node revealed histologic changes of Hodgkin's disease

3 Nodules and Tumors A further division of specific cutaneous Hodgkin's disease is the primary or initial lymphogranulomatous cutaneous lesion which first develops in the skin proper and is not merely an extension from a deeper lesion of a contiguous lymph node The primary lesion may be a nodule infiltration or specific ulcer French investigators have



26 Nodule on the conjunctiva
27 Hodgkin's tumor of the scalp (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

designated this lesion "Le Chancre Lymphogranulomateux" Thus Hodgkin's disease would have a primary lesion such as occurs in tuberculosis syphilis sporotrichosis and other conditions

It was the opinion of Nanta and Chatellier (239c) that there is often an inoculation lesion in Hodgkin's disease They de

scribed two cases The first patient developed a thickened lesion on the dorsum of the tongue three years before the lymph node involvement Histologic study of the tongue lesion was not conclusive but the lymph node picture was typical for Hodgkin's disease The second patient had developed a large tumor on the dorsum of the hand two years before lymph node involvement became apparent Histologic examination showed Hodgkin's disease in both the cutaneous tumor and the lymph node One of Miller's (224a case 3) patients, who had a definite history of tuberculosis, developed a solitary nodule on the buttock one year before other cutaneous lesions appeared The similarity of these lesions to those of mycosis fungoides "d'emblee" is one of the many reasons for the existing confusion regarding the "d emblee" form of mycosis fungoides

The patient described by Favre *et al* (100b) developed a "hazel nut' sized lesion following puncture of the skin of the popliteal fossa The lesion was removed surgically after it became ulcerated and histologic examination revealed Hodgkin's disease Fuchs (111) reported a 42 year old man who had a granulomatous lesion of the nares and nasal passages which caused obstruction On the tip of the nose was a thick "trumpet like' swelling and the bridge of the nose was destroyed by the process This condition had been diagnosed as "tuberculosis four years previously and was apparently cured by curettage However the disease recurred two years later when a diagnosis of syphilis" was made and he was treated with salvarsan The condition remained unchanged and a diagnosis of lupus vulgaris was made and he was given roentgenotherapy The external nasal lesions cleared up within three weeks but recurred soon after There was a red nodular mass exhibiting both proliferative and destructive changes in the skin and underlying tissue and roentgenograms revealed a shadow in the nasal passages nasopharynx and both antra The skin was reddened for some distance around the nasal lesion There were some hard cervical lymph nodes and fever Although the histologic picture was not conclusive carcinoma with concomitant erysipelas was suspected Fol

lowing roentgenotherapy to the face and neck his general health improved and the external nasal lesion cleared almost completely Four months later he had developed submandibular cervical axillary and inguinal lymphadenopathy There were 17 per cent eosinophils in the peripheral blood He died six weeks later and histologic examination of the nasal lesions and lymph nodes showed replacement of the lymph follicles by epitheloid cells with a few scattered Sternberg Reed and plasma cells

The first manifestation of Hodgkin's disease was an ulcerative lesion on the heel in the case reported by Kren (178b) Cutaneous infiltration of the extremities occurred later and lymphatic dissemination followed Cases of this type were also described by Arndt (9b) Arzt and Randak (10f) Reinsberg and Kadlicky (272) and Saalfeld (285)

The scalp appears to be a frequent site of the initial lesion in cutaneous Hodgkin's disease Greenhouse and Cornell (130) described by Arndt (9b) Arzt and Randak (10f) Reinsberg months previously Three months after the trauma a small "pimple" appeared on the vertex of the scalp which gradually increased in size There was a roughly circular 7 5 cm area of alopecia about half of which was occupied by a sharply outlined "palm" sized serpiginous smooth shiny indurated lesion which was raised 0 5 cm above the skin surface and of a bluish red slightly yellow color The lesion was painless and freely movable The histological picture was typical of Hodgkin's disease The lesion responded rapidly to roentgenotherapy and completely disappeared No new lesions occurred for seven years A woman who carried "heavy burdens" on her head was reported by Dossekker (84) She developed a tumor of the scalp which was histologically Hodgkin's disease Jessner (165) later stated that the lesions spread on the scalp and over the body after one year and were followed by lymphadenopathy She died several years later and the diagnosis of generalized Hodgkin's disease was confirmed at autopsy Primary Hodgkin's disease of the scalp was also described by Pollock (262)

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The patient described by Favre *et al* (100b) developed a "hazel-nut" sized lesion following puncture of the skin of the popliteal fossa The lesion was removed surgically after it became ulcerated and histologic examination revealed Hodgkin's disease Fuchs (111) reported a 42 year old man who had a granulomatous lesion of the nares and nasal passages which caused obstruction On the tip of the nose was a thick "trumpet like" swelling and the bridge of the nose was destroyed by the process This condition had been diagnosed as "tuberculosis" four years previously and was apparently cured by curettage However the disease recurred two years later when a diagnosis of syphilis' was made and he was treated with salvarsan The condition remained unchanged and a diagnosis of 'lupus vulgaris' was made and he was given roentgenotherapy The external nasal lesions cleared up within three weeks but recurred soon after There was a red nodular mass exhibiting both proliferative and destructive changes in the skin and underlying tissue and roentgenograms revealed a shadow in the nasal passages, nasopharynx and both antra The skin was reddened for some distance around the nasal lesion There were some hard cervical lymph nodes and fever Although the histologic picture was not conclusive carcinoma with concomitant erysipelas was suspected Fol-

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after but subsided under arsenotherapy However numerous purplish nonulcerating tumors resembling "leprous nodules or large syphilitic papules" then appeared They resolved under roentgenotherapy leaving a brownish pigmentation Histologic studies of the lymph nodes and cutaneous tumors revealed Hodgkin's disease Fox's (106) patient was a 30 year old man who had moderate painless lymphadenopathy hepatosplenomegaly mild anemia dyspnea on exertion and increasing asthenia for 15 months Histologic examination of a lymph node revealed unicellular and multicellular giant cells of the Sternberg Reed type There were tumor like infiltrations of portions of the scalp forehead and midscapular region and the scalp lesion had the same histologic structure as the lymph node

In reviewing the reports of cutaneous nodules or tumors having the characteristic histological picture of Hodgkin's disease Hovelborn (155) found 68 cases had been recorded up to 1932 Numerous cases have been described since that time

In 1909 Hecht (141) described a 32 year old man who had cervical and axillary lymphadenopathy The right side of the face was edematous and "tumor like" and the eyelids were edematous The skin and connective tissue of the neck later became infiltrated by the tumor There were small scattered elevated purple areas having a pink halo on the thorax and somewhat larger tumors above the left scapula and on the sacrum The peripheral blood revealed slight eosinophilia and histologic examination of a cutaneous tumor disclosed Sternberg Reed cells A 39 year old man reported by Rusch (284) had multiple inguinal lymphadenopathy some nodes were of "apple" size and there were palpable abdominal lymph nodes Five weeks before death he developed 30 to 40 hard nodules in the deep cutis of the inner aspects of the thighs the abdomen and over the trochanters This exanthem began as "red spots" but developed to become rose to dark red and livid in color and finally became hemorrhagic The cutaneous tumors and lymph nodes showed the typical histologic picture of Hodgkin's disease

Two patients who had a single cutaneous tumor were described by Gates (116). A 12 year old boy who developed a small, firm, "hickory nut" sized nodule following slight trauma was reported by Wrong (356). The lesion disappeared following roentgenotherapy. Trimble's (327) patient was a 40



28 *Subcutaneous Hodgkin's nodules*

year old man who had cutaneous lesions on the side of the neck which resembled lupus vulgaris. Histologic examination of the lesion revealed Hodgkin's disease. Nobl (245a) described a young woman who had massive cervical and axillary lymphadenopathy which required surgical excision. A diffuse red cutaneous edema of the left side of the thorax occurred soon

tous pleomorphism plus the tendency to fibrosis and necrosis

case (287 case 23) in a 64 year old Negro who had pruritus and multiple, "pea" sized subcutaneous nodules involving the entire body, and back pain/

The patient reported by Louste *et al* (201) was a 25 year old woman who had cutaneous and subcutaneous nodules on the face and arms She had cervical and preauricular lymphadenopathy, 11 per cent eosinophils in the peripheral blood and roentgenogram of the chest revealed hilar node involvement Histologic examination of a lesion on the forearm showed Hodgkin's disease Two patients who presented cutaneous nodules as the first symptom of Hodgkin's disease were described by Van der Meiren (330) The first was a 45 year old woman who presented two types of cutaneous lesions on the face There were erythematous areas with telangiectases and oval or hemispherical firm nodules, both present for one year, which were pruritic on "sunny days" Histological examination revealed a continuous infiltration of polymorphonuclear inflammatory cells, including numerous Sternberg Reed cells, under the atrophic epidermis Roentgenotherapy resulted in healing of some of the lesions but there was no lymph node or visceral involvement three years after onset of the disease Their second patient was a 57 year old man who had been treated for lichenified eczema of the left arm for several years before tumor like lesions appeared in this area There were numerous hemispherical nodules scattered on a dark lichenified skin on the left elbow, some of which extended into the normal skin and there was a larger tumor composed of several confluent nodules on the outer aspect of the arm Histologic examination of these tumors disclosed Hodgkin's disease Six years later another tumor appeared on the left forearm which was histologically similar to the previously examined lesion He died six years after onset of the illness from a disease unrelated to Hodgkin's disease

Rulison (283a) described a 30 year old man with specific cutaneous lesions of Hodgkin's disease He had moderate painless lymphadenopathy, hepatosplenomegaly, mild anemia dyspnea on exertion, and increasing asthenia The cutaneous lesions consisted of tumor-like infiltrations of the scalp, forehead and midscapular region The histologic picture of these tumors and the lymph nodes showed similar structures

A 29 year old man who had "psoriasis" for the previous nine years was described by Ross (278) Small raised nodules had appeared on the arms and chest during that time and had occasionally ulcerated The skin was hard and scaly with some ulceration, particularly over the chest and arms, where numerous firm, raised, pink nodules were present There was marked cervical and inguinal lymphadenopathy Despite roentgenotherapy to the posterior mediastinum, dyspnea was progressive, a pleural "rub" developed and he died of pulmonary involvement Histological examination, at autopsy, disclosed the cutaneous lesions of the chest and arms to be Hodgkin's disease and two lesions were found in the left pectoral muscle

Sahyoun and Eisenberg (287) attempted to classify Hodgkin's disease, exclusive of Hodgkin's sarcoma, on a correlative basis between the histopathologic criteria and the clinical course They listed the following three types

1) The compactly cellular type which is slowly progressive, having a maximum life expectancy of four to 13½ years

2) The fibrogranulomatous type which is moderately progressive having a maximum life expectancy of approximately two to five years

3) The loosely cellular type which is rapidly progressive, having a maximum life expectancy of about one to one and one-half years

In group one the characteristic cytologic differential features are the compact structure of the tumor with only slight fibrosis They (287 case 11) described a 40 year old Negro who had cutaneous pruritus, which occurred only at night, and multiple diffuse subcutaneous nodules as illustrative of this form The cytologic differential features of group two are the granuloma-

after the appearance of the first symptoms Gadrat's (114b) patient was a 34 year old woman who developed a cutaneous nodule without visceral or glandular symptoms The nodule was excised and one year later a similar nodule appeared in another area which showed the histologic structure of Hodgkin's disease There was no further evidence of the disease three years after the original lesion had appeared A patient having cutaneous Hodgkin's disease without glandular involvement for 20 years was reported by Favre (100i)

A 60 year old man who had numerous small cutaneous tumors resembling mycosis fungoides was described by Dujardin and Van de Meiren (88) The lesions showed the typical histologic picture of Hodgkin's disease although generalized lymphadenopathy did not occur until shortly before death five years later Geipel and Linser (117) reported a 22 year old man whose first symptom was the development of small nodules on the scalp in close relation to the hair follicles and containing central infected necrotic areas As the disease progressed the small nodules fused forming large plaques covered with scales Three years later the process had extended to involve the face and resembled acne The lesions developed from the follicles and showed an inflammatory process in the sweat glands at the onset of the disease

The 37 year old patient reported by Rosti (280) developed the primary tumor near the sternum but there was no associated lymphadenopathy A 38 year old man described by Baum (19) developed nodules on the right upper arm followed by other lesions on the trunk and outer arm which were hard and larger than a "cherry" in size Cannon's (56b) patient was a woman who developed several "orange sized" subcutaneous masses in the left inguinal region They were non tender irregular in shape and composed of a number of "lumps" matted together and bound down to the underlying surface while the overlying skin was freely movable There were smaller firmer masses in the right groin The histologic examination revealed Hodgkin's disease A 52 year old man who had a generalized eruption of pink macules and petechiae

A 67 year old woman who developed a rapidly growing cutaneous lesion in the left submaxillary region was described by Gross (131) This firm, 'quarter dollar' sized, purple tumor had been present for three months and extended into the subcutaneous tissue, but was freely movable Histologic examination disclosed the typical picture of Hodgkin's disease There was a granuloma in the corium, with hypertrophy of the reticulum and an infiltrate consisting of lymphocytes and plasma cells, scattered eosinophils and numerous Sternberg-Reed cells having two or three nuclei Dupont (89b) described a 29 year old man who died of Hodgkin's disease At autopsy a small nodular cutaneous tumor of the chest was found which had the histologic picture of Hodgkin's disease as well as of tuberculosis

The first patient reported by Jordan et al (167) was a 23 year old man who had headache, insomnia and weakness for three months The only physical findings were a nontender swelling of the forehead and a perforation of the septum which was caused by his "snuffing" cocaine Despite negative serological tests, the diagnosis was assumed to be tertiary syphilis Antisyphilitic therapy, however, caused increasing weakness and lymphadenopathy and fever occurred The diagnosis of Hodgkin's disease was confirmed at autopsy

Falconer and Leonard (98 case 5) described a 45 year old man who had a swelling of the neck for four months when histologic examination of a lymph node disclosed Hodgkin's disease Roentgenogram of the chest revealed small parenchymatous shadows in the right upper lobe of the lung and he was given roentgenotherapy Four months later he developed pressure in the throat which interfered with breathing and swallowing He also had sharp pain in the left chest region, associated with dyspnea and an unproductive cough Fluid was aspirated from the left pleural cavity and roentgenograms showed widening of the mediastinum above the aorta as well as peribronchial infiltration in the left lower lobe of the lung He also had cutaneous lesions which had the histologic structure of Hodgkin's disease He died two years





29 Nodular lesions of Hodgkin's disease (case report) (courtesy of H Steinberg MD)

30 Nodular lesions of Hodgkin's disease (case report) (courtesy of H Steinberg MD)

lowed by weakness loss of weight and occasional transient pains in the right leg and lower back Following deep roentgenotherapy the lymphadenopathy disappeared and his general health improved However several weeks later he developed fever chronic fatigue and the pain became more severe Three months after therapy he developed a painless swelling of the left nipple followed by left cervical axillary and right inguinal lymphadenopathy There was swelling in the left temporal and temporal mandibular regions This latter area became tender and he developed headaches The lymphadenopathy increased and multiple cutaneous nodules appeared There was a firm 0 5 cm sized nodule on the xiphoid process in the midline and a similar nodule on the left lateral aspect of the knee The skin in the cervical region was of a darker color than that of other areas A productive cough and night sweats developed and rapidly increased in severity At autopsy the skin was dry and contained numerous hard nodules The larger

as well as superficial cervical and inguinal lymphadenopathy, was reported by Bram (41) There were a few cutaneous and subcutaneous nodules of the face which resulted in a leonine appearance These nodules, up to 1 cm in diameter, were firm, painless and nontender, while some appeared to be unattached to the skin or to the deep fascia There was purpuric staining over some of these nodules Similar cutaneous and subcutaneous nodules then appeared on the upper extremities and trunk, but were almost entirely absent on the legs Histologic examination of a nodule revealed a granulomatous structure with some central necrosis

Lees and Edgeworth (186) described a 52 year old man who had lymphoid growths* in the orbits eyelids temporal regions and left mammary area He had developed swelling of the right side of the neck four months previously, followed by swelling of the right axilla and inguinal region left side of the neck, axilla and groin The spleen was palpable and the tonsils and pharyngeal lymph nodes were enlarged Death occurred 11 months after onset of the illness Reinsberg and Kadlicky (272) reported a 59 year old woman who had unilateral cervical and submaxillary lymphadenopathy which resulted in deformation of the left side of the neck There were five freely movable, pliable, elastic tumors of "pigeon's egg size in this area and flattened semi transparent symmetrical nodules involving the upper and lower third of both eyelids The monomorphous cutaneous eruption consisted of 'millet grain sized follicular nodules which were disseminated on the cutaneous surface, and were either isolated or augmented in plaques Milian *et al* (223e) described a patient who had a large vegetating penile lesion accompanied by bilateral inguinal lymphadenopathy The lesion simulated epithelioma The histologic diagnosis was Hodgkin s disease and intensive roentgenotherapy resulted in rapid involution

Case Report A 27 year old Negro first developed left cervical lymphadenopathy seven months previously which was fol

* See Illustration 26





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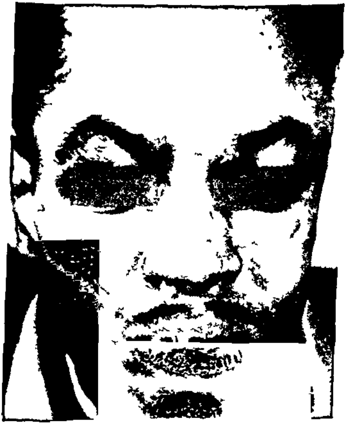
Case Report This patient, a 67 year old man first developed numerous 1 cm sized ulcerated draining nodules involving the right inguinal region and the greater portion of the thigh two months previously There were large patches of "eczematous" eruptions on the trunk arms and legs There was a brownish pigmentation and edema of the right leg The nodules gradu



32 Nodular Hodgkin's disease of the right groin (case report) (Bluefarb and Schwartz *Arch Dermat.*, Feb 1956)

ally spread to involve the genitalia and three months later a hard tender mass developed in the preauricular region He was given roentgenotherapy and nitrogen mustard but did *not* improve At the onset of his illness the hemogram revealed 67 per cent hemoglobin 3 800 000 red blood cells and 14 300 white blood cells per cu *mm* with 86 per cent polymorphonu clears 11 per cent lymphocytes and 3 per cent monocytes However before death five months later the hemoglobin was 25 per cent red bood cells 1 370 000 and white blood cells 1 000 per cu *mm*

ones were present on both tibia and thighs and on the right flank left chest and paravertebral regions A mass of nodules involved the right clavicular area There were hard discrete palpable lymph nodes in the axillary and inguinal regions There was marked cutaneous pigmentation in the cervi



31 Nodular lesions of Hodgkin s disease (case report) (courtesy of H Steinberg M D)

cal and anterior chest areas The autopsy diagnosis was Hodgkin s disease with sarcomatous features involving the liver spleen pancreas skin ribs left testicle and cervical axillary and peribronchial lymph nodes as well as pulmonary tuberculosis





34 Ulceration of the skin due to Hodgkin's disease of underlying lymph nodes

35 Ulceration of the skin due to Hodgkin's disease of underlying lymph nodes

4 *Ulcerative Lesions* Ulcerative cutaneous lesions are an infrequent but important form of specific involvement in Hodgkin's disease In a comparative review of this subject Senear and Caro (294b) described three initial forms which occur in this type In the first the ulceration is limited in extent and develops in a few cutaneous nodules with the necrosis usually starting at the top of the nodule and gradually extending until the surface of the nodule is almost completely covered * In the second type cutaneous involvement results from lymphogranulomatous changes in the underlying structures The involved lymph nodes or underlying structures



33 Ulceration of the skin due to Hodgkin's disease of underlying lymph nodes (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

such as bone or other tissues gradually become inflamed adhere to the skin and then form fistulae leading to ulceration The third type presents extensive ulceration developing in large cutaneous infiltrations without involvement of the underlying structures This type has been confused with mycosis fungoides d'emblee since the cutaneous lesions may precede

* See Illustration 32

"pea to walnut size" in the right clavicular region Some nodules ulcerated and coalesced to form a "saucer sized" ulcer which had the histologic picture of Hodgkin's disease A similar case reported by Parkhurst (252) was a 31 year old man who had Hodgkin's disease with lymphadenopathy for four years before he developed a nodule on the calf of the left leg Other nodules subsequently appeared and there was a clean shallow undermined ulcer surrounded by an erythematous infiltrated margin on the right calf There was a "dime sized" erythematous infiltrated intracutaneous nodule on the scrotum and a smaller similar nodule anterior to the left ear The patient described by Sweitzer and Winer (319b) developed lymphadenopathy which receded within a few weeks but recurred two months later and persisted Six months later a small nodular pruritic eruption developed on the left thigh which became ulcerated because of persistent excoriation The leg was edematous during the day but subsided after bed rest On admission he presented inguinal lymphadenopathy and numerous 1 to 3 cm sized ulcers on the left thigh These ulcers began as small papules which disintegrated and eroded then enlarged and coalesced and showed no tendency to spontaneous healing They were freely movable slightly tender and had elevated indurated sharply defined borders and granulating purulent covered bases Some smaller ulcers which had brownish crusts had a purulent base on removal of the crust There were several nonulcerated papules interspersed between the ulcers The histologic diagnosis was ulcerative Hodgkin's disease of the skin

Another case of this type was a 54 year old man reported by Shelmire (298 case 2) He had many "bean sized" brownish cutaneous tumors of the neck and right side of the thorax Some tumors were ulcerated in the center and there was marked cervical supraclavicular and axillary lymphadenopathy A clinical diagnosis of acute acne cachecticorum was made Histologic examination of a cutaneous nodule revealed a mass of granulation tissue extending from the thin epidermis into the lower portion of the cutis This tissue completely replaced the normal connective tissue and showed a polymorphous cell

the lymphadenopathy or visceral manifestations by a period of months to many years

Sweitzer and Winer (319b) also classified the ulcerative lesions as 1) The Grosz or Hirschfield type having cutaneous ulcerative lesions the ulceration is limited in extent and develops in small cutaneous nodules 2) The Cole Anderson type exhibiting extension from lymph nodes bones or other tissue and 3) The Doessecker Kren Saalfeld type in which the skin is the primary focus of Hodgkin's disease In the first type



36 Large tumors of Hodgkin's disease simulating mycosis fungoides D emblee (Bluefarb and Schwartz *Arch Dermat* Feb 1956)

ulceration develops in a number of cutaneous or subcutaneous nodules which have the typical histopathologic structure of the disease Grosz (133) was a typical example of this form in which the necrosis usually begins on the top of a nodule and gradually extends to cover the surface of the nodule more or less completely The lesions may remain discrete or may coalesce to form large ulcers Hirschfeld (151) described such a patient who developed numerous brownish red nodules of

nodules subsided leaving pigmented scars but some ulcerated and were covered with dark brown macules The specific cutaneous lesions in this case preceded other manifestations of Hodgkin's disease and the clinical picture resembled Weber Christian disease

The second type of ulcerative cutaneous lesions resulting from secondary involvement of underlying structures are illustrated by the following cases The first case of ulcerative cutaneous Hodgkin's disease reported in the United States was that of Alderson (6) This 28 year old man developed cervical and axillary lymphadenopathy which was histologically typical of Hodgkin's disease Two years later a painless oval swelling appeared along the middle third of the right tibial area and a similar hard swelling apparently connected with the periosteum appeared on the lower third of the left leg over the tibia Four months later the indurated lesions broke down and formed ulcers clinically indistinguishable from a gumma which showed Hodgkin's disease of the subcutaneous tissue and skin on histologic examination A 37 year old man reported by Cole (64a) had a swelling of the right supraclavicular region which was believed to be an "abscess" Lymphadenopathy in this region alternately appeared and disappeared and histologic examination revealed Hodgkin's disease The lymphadenopathy continued and several lymph nodes eventually ulcerated The only cutaneous lesions were a large irregularly rhomboid mass 3 by 5 cms in size in the right supraclavicular region which was indurated centrally ulcerated and apparently fused to the underlying lymph nodes There were several "hickory nut" sized lesions to the distal side of this area some of which had ulcerated

Dupont (89a) described a 29 year old man who had cervical lymphadenopathy and the left pectoral region was elevated There was a "palm sized" irregularly outlined indefinitely polycentric plaque which was composed of nipple like projections covered by glossy dull red skin in the center of the elevation and the furrows and depressions separating the projecting buds were ulcerated in some areas The cutaneous and

infiltration composed of lymphocytes, plasma cells, eosinophils and the characteristic multinucleated giant cells of Hodgkin's disease The patient described by Sniegowski (312) had multiple flat, bright red cutaneous nodules on the thoracic wall Some lesions became necrotic, formed ulcers with an erythematous halo, and coalesced to involve an area extending from the right axillary to the left mammary line This area was, for the most part, covered with a blackish brown crust having sharp borders and was not undermined A woman described by Bine (30) developed cutaneous nodules which disappeared spontaneously within a week However, eight months later, nodules which broke down and ulcerated appeared on the hard palate One nodule assumed a punched out character and suggested a lesion of late syphilis There was a sloughing lesion involving the opposite side of the palate which perforated, and sloughing of a long-standing hemorrhoidal lesion also occurred The autopsy diagnosis was Hodgkin's disease of the spleen, liver, kidney, adrenal glands and bone marrow There were no palpable superficial lymph nodes but necrosis and infiltration were present in one lymph node over the head of the pancreas

A 59 year old man, reported by Senear *et al* (249c), had a generalized cutaneous eruption which spared only the palms, soles and genitalia There were many large, soft, purplish red nodules on the dorsal surfaces of the feet and on the legs, thighs and buttocks, with considerable brownish pigmentation Large, but less profuse, nodules were present on the backs of the hands, the forearms and arms and large ulcerated nodules over the right eyebrow and lobe of the left ear, many of which were ulcerated and crusted Histologic examination of a nodule from the arm and the lymph nodes revealed Hodgkin's disease The patient described by Nanta (239a) developed an ulcer at the naso labial commissure which extended over the cheek In Chevallier and Bernard's (62) patient, the ulcer appeared in the perineal region The case reported by Reimann *et al* (271) was a 45 year old man who developed nodules on the chest and abdomen The majority of these

nodules subsided leaving pigmented scars but some ulcerated and were covered with dark brown macules. The specific cutaneous lesions in this case preceded other manifestations of Hodgkin's disease and the clinical picture resembled Weber Christian disease.

The second type of ulcerative cutaneous lesions resulting from secondary involvement of underlying structures are illustrated by the following cases. The first case of ulcerative cutaneous Hodgkin's disease reported in the United States was that of Alderson (6). This 28 year old man developed cervical and axillary lymphadenopathy which was histologically typical of Hodgkin's disease. Two years later a painless oval swelling appeared along the middle third of the right tibial area and a similar hard swelling apparently connected with the periosteum appeared on the lower third of the left leg over the tibia. Four months later the indurated lesions broke down and formed ulcers clinically indistinguishable from a gumma which showed Hodgkin's disease of the subcutaneous tissue and skin on histologic examination. A 37 year old man reported by Cole (64a) had a swelling of the right supraclavicular region which was believed to be an "abscess." Lymphadenopathy in this region alternately appeared and disappeared and histologic examination revealed Hodgkin's disease. The lymphadenopathy continued and several lymph nodes eventually ulcerated. The only cutaneous lesions were a large irregularly rhomboid mass 3 by 5 cms in size in the right supraclavicular region which was indurated centrally ulcerated and apparently fused to the underlying lymph nodes. There were several "hickory nut" sized lesions to the distal side of this area some of which had ulcerated.

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visceral involvement was typical of Hodgkin's disease and the cutaneous lesions exhibited the coexistence of typical lymphogranulomatous and tuberculoid lesions on histologic examination.

It was the opinion of Gadrat (114a) that in cases of this type the massive tissue destruction is of lymph node origin, the glands having literally poured out their lymphogranulomatous infiltrate into the deep layers of the skin, the tissues being eventually destroyed by necrosis. The skin is thus undermined and destroyed just as are bones and muscles in Hodgkin's disease.

Etienne *et al* (95) described a 35 year old woman who had two large ulcers with rather sharp violaceous contours and everted margins in both cervical regions. These ulcers followed the development of a fistula caused by necrosis of underlying lymph nodes due to Hodgkin's disease. Three patients having ulceration were described by Arzt and Randak (10f). The first was a 52 year old man who developed axillary lymphadenopathy followed by cutaneous ulceration and phlegmonous infiltration of the abdomen and chest. The second patient was a woman who had axillary, submaxillary and supraclavicular lymphadenopathy. The growth in the left axilla became edematous and formed a destructive ulceration with thickened borders and a granulation tissue covered base. The third patient developed occipital lymphadenopathy with subsequent suppuration. An ulcer appeared in this region which gradually increased in size and depth to involve the entire right side of the scalp and neck until the vessels and bones were exposed. This patient died within one year and autopsy disclosed Hodgkin's disease. There was slight involvement of the superficial lymph nodes but the occipital bone was nearly destroyed at the base of the ulcer and the dura was infiltrated by granulomatous tissue. Linser (193) observed a 35 year old woman who had multiple lymphadenopathy associated with diffuse ulceration of the axillary and cervical regions.

A 23 year old man described by Senear and Caro (294b) had moderate lymphadenopathy of the axillae, left inguinal

posterior left auricular and left kidney region. He developed a well defined deep irregularly outlined somewhat elevated ulcer in the right maxillary region which extended horizontally from the posterior axillary line to the nipple line and vertically from the level of the fourth interspace to the shoulder. The overlying tissue was firmly adherent and the base was bright red, uneven, friable and covered with a foul purulent exudate with a firm broad surrounding zone of induration. Despite roentgenotherapy his condition rapidly deteriorated and the entire right chest showed a "board like" infiltration. A similar infiltration developed in the right supraclavicular region and the overlying skin was mottled red and painful. A similar but smaller ulcer developed in the right infraclavicular region within two weeks time. The characteristic histologic picture of Hodgkin's disease was present in the cutaneous ulcer, lymph nodes of the anterior thoracic wall and mediastinum.

Famelle and Neujean (99) reported a 32 year old man who had a painful swelling over the sternum for ten weeks. This swelling increased in size and finally formed a painful ulcer with an irregular base which bled easily and the underlying bone became eroded. Histologic examination of an involved lymph node and a portion of an ulcer showed the typical picture of Hodgkin's disease. A woman who developed an excoriating ulcer the size of a "small hand" at the base of the neck follo[illegible]

[illegible] in osteomyelitis in the manubrium was described by Pessin and Pohle (257). She had a shiny ulcerated nodule on the left side of the chest. Roentgenogram revealed a "moth eaten" appearance of the lower left half of the manubrium and lateral to and below this area was a poorly defined area of increased density which extended between the first and second ribs. Curettage of the manubrium disclosed a small localized abscess with brawny induration of the subcutaneous tissues which had a greenish yellow exudate. The gross specimen consisted of greyish yellow and greenish yellow "jelly like"

tissue and a few fragments of fibrous tissue A granulomatous mass subsequently developed at the site of the surgical incision and a red, raw, firm, elevated cutaneous tumor appeared in this region Histologic examination of a lymph node revealed Hodgkin's disease

Middleton (221 case 4) reported a 26 year old woman in whom histological examination of an axillary lymph node had been diagnostic of Hodgkin's disease three and one half years previously The biopsy wound, however, had not healed and cervical lymphadenopathy subsequently appeared Extensive roentgenotherapy was given but involvement of the left breast occurred and extension from the original site was suspected The process was fairly well controlled with roentgenotherapy except for mild exacerbations in the primarily involved areas However, 27 months later, there was a progressive lymphadenopathy and a draining sinus in the right upper chest During the next 14 months the ulceration extended somewhat into the right infraclavicular region These ulcers showed a 'dirty grey base' with abrupt margins and, subsequently, another supraclavicular sinus appeared These two areas eventually joined to form a single ulcer, 10 by 12 5 cms in size, with a slightly sluggish granulation of the edges Krueger and Meyer (179) reported two patients who had cutaneous ulceration over enlarged lymph nodes

Autopsy study on Lyons (204) patient disclosed an irregular, somewhat oval shaped ulcer 130 by 100 mms in size, which extended into the right chest cavity A considerable portion of the sternum and adjacent portions of the ribs and right clavicle were eroded and the cutaneous surface of the edges of the opening were covered with normal epidermis, beneath which was what appeared to be newly formed fibrous tissue The pleural surface of the edges of the opening appeared to be composed of infected and necrotic tissue The exposed ends of the bone were eroded and necrotic The chest opening appeared to have been formed primarily from pressure necrosis and the continued enlargement appeared to have occurred in

part at least by necrosis of the skin and subjacent tissue imme diately behind the edges of the opening

Dobes and Weidman (83) reported a 35 year old Negro who had developed deep ulcerated granulomas in the cervical lymph nodes and skin during the preceding three or more years The ulcerations began in the left cervical region became con centrated on the left thoracic wall and finally extended to the right breast Generalized lymphadenopathy and intermittent fever eventually developed and anemia gradually appeared The red blood cells numbered 3 450 000 per cu mm with 52 per cent hemoglobin and eosinophilia (absent at first) reached 84 per cent Intensive roentgenotherapy caused a definite although temporary improvement The histologic picture was not diagnostic and there was at first no tissue eosinophilia although it later became extreme The histologic picture was "atypical for a considerable period before the lymph node histologic picture proved to be characteristic of Hodgkin s disease

The case reported by Levin and Behrman (189) was a 32 year old Negro who developed numerous firm tender nodules of "pea to quarter dollar" size on the chest over the manu brium sternum These lesions gradually became confluent and ulcerated superficially in the central portion Roentgeno therapy was administered and the lesions at first responded to treatment but later became radio resistant and numerous keloidal nodules developed around the original sternal cutane ous lesions as well as in the clavicular and axillary regions Traut (326) described a 57 year old man who had a spon taneous fistula The cervical lymph nodes had become fluctu ant and exuded a "cheesy" material Another fistula de veloped at the site of a biopsy incision and another in a left axillary swelling In Linser s (193) case the cutaneous infil tration also followed incision of a lymphogranulomatous swelling

Senear (294a) described two cases of this type of ulceration The first patient (294a case 4) was a 23 year old woman who had a firm supraclavicular lymphadenopathy of the left side

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typical of Hodgkins disease but this diagnosis was established at autopsy A 40 year old man who developed a tumor of the right heel was reported by Kren (178a) Inguinal lymphadenopathy occurred and the tumor became ulcerated assuming a "sarcoma like" appearance The leg was amputated but two years later there were "hazelnut to walnut" sized cutaneous nodules which were more marked on the extremities These lesions tended to ulcerate and one over the left patella degenerated into a serpiginous ulcer The diagnosis was made at autopsy

The patient described by Saalfeld (285) was a 52 year old man who had left axillary lymphadenopathy which broke down

had irregular outlines and elevated margins reached a considerable size and eventually the brachial plexus and blood vessels were exposed *Histologic examination disclosed* Hodgkins disease A 41 year old man who developed infiltrated lesions in the region of enlarged clavicular lymph nodes was described by Grossman and Schlemmer (132) These livid ulcerated lesions also involved the left arm and knee and later appeared in the occipital region left side of the neck and on one thigh

The patient reported by Arzt (10a) was a 25 year old man who had a 3 by 10 cm ulcer in the right occipitonuchal region This lesion had appeared one year previously accompanied by cervical lymphadenopathy and had spread progressively despite treatment The ulcer had sharp firm borders and a rough purulent necrotic base which reached the bone The adjoining lymph nodes were palpable There was a peripheral blood eosinophilia of 5 per cent The ulcer extended to involve the muscle and bone and there was considerable sloughing The favored clinical diagnosis was mycosis fungoides "d emblee" but autopsy revealed granulomatous processes with circumscribed nodules in the lymph nodes liver and spleen The histology of these organs and a cutaneous ulcer revealed

This nodule had been removed surgically one year previously when a diagnosis of "a manifestation of a lymphogranuloma" had been made and roentgenotherapy instituted Five months later she presented cervical and axillary lymphadenopathy and a roentgenogram of the chest revealed mediastinal involvement Three months later she had developed a linear, ulcerative lesion of the right side of the neck in an area where there was slight drainage The skin in this area overlying the enlarged cervical lymph nodes had been infiltrated for some time The clinical diagnosis at this time would unquestionably have been "scrofuloderma" but, in view of the previous history, the neck lesions were examined histologically and the typical picture of ulcerative Hodgkin's disease was apparent Another patient (294a case 2) was a 57 year old woman who had developed swelling in the right axilla three months previously and, one month later, anorexia weight loss and weakness occurred On admission she had marked submaxillary and right cervical lymphadenopathy and a painful, "walnut" sized lymph node in the right supraclavicular region There was a vegetating "tomato sized mass in the right axilla which was necrotic ulcerated, and of a bright red color with a tenacious yellowish discharge There was a 3 cm ulcer on the thoracic wall just below this lesion The histologic picture of a lymph node revealed typical Hodgkin's disease and a large, vegetating ulcerative cutaneous mass showed an identical picture

The third type of ulceration develops in the skin either as a primary manifestation of the disease or secondary to it, not as a direct extension of lymphadenopathy large infiltrates or tumors

Dossekker (84) described this type of ulceration in a 54 year old woman whose first manifestation of the disease was a painless swelling of the scalp Later infiltrations and flat tumors developed on the forehead followed by superficial "walnut to pigeon's egg size ulcerations which resembled mycosis fungoides Cervical and occipital lymphadenopathy occurred later and a well defined deep ulcer developed over the ear The histologic picture of the cutaneous lesions was not

This ulceration extended to involve the entire right axilla within the following three months The autopsy diagnosis was Hodgkins disease of the lymph nodes and cutaneous ulcerated areas and the breast tumor showed granulation tissue with innumerable Sternberg Reed cells

A 42 year old woman who had superficial painless ulcerations scattered evenly over the trunk and extremities was described by Czezowska and Mierzecki (75) These lesions showed no tendency to coalesce and similar though less severe lesions were present in the mouth Following roentgeno therapy to the mediastinal nodes the ulcers of the upper extremities and thorax disappeared and those of the lower extremities cleared following irradiation of the abdomen However the mediastinal tumor enlarged and there was an elevation of body temperature as her general physical condition declined and numerous cutaneous lesions became confluent forming a large deep ulcer over the tibia tarsal joint Despite treatment this ulcer increased in width and depth and a profuse hemorrhage developed which necessitated amputation above the joint Histologic examination of the ulcer showed Hodgkins disease with numerous Sternberg Reed cells

Ginsburgs (121b) patient was a 54 year old woman who had two "punched out" ulcerations of the right breast and hemorrhagic cutaneous infiltration of the chest Histologic examination revealed Hodgkins disease A patient having three confluent ulcerations on the neck and one below the ear was described by Moraime (231) There was multiple lymphadenitis most marked in the right parotid region Histologic examination of the ulceration revealed Hodgkins disease Localized [illegible] ion of the [illegible] with a ter [illegible] through the blood stream was reported by Bersack (27b) This 44 year old man first developed a "lump" on the right calf which grew to "hens egg" size became ulcerated and was followed by new ulcerated lesions The histopathologic picture of the older lesions revealed Hodgkins dis

lymphocytes, plasma cells and Sternberg Reed cells Gadrat (114a) described a 52 year old man who developed a "hazel nut sized swelling" on the lower jaw one year previously The nodule grew to the size of an "orange" while the overlying skin became thin, ulcerated and ruptured, discharging a gangrenous exudate Histologic studies showed Hodgkin's disease The cutaneous lesions in Milian's (223a) patient suggested early mycosis fungoides Extensive cervical and subclavicular tumors, many ulcerated, developed and the borders of these ulcers showed innumerable Sternberg Reed cells on histologic examination A 39 year old woman who had a generalized cutaneous eruption resembling mycosis fungoides was described by Mousson (233) Cervical lymphadenopathy developed and several large deep ulcers appeared on the forehead, scalp and shoulder These sharply marginated ulcers presented a "dirty base" and were surrounded by a flat infiltrated zone The histologic picture was Hodgkin's disease

Laederich *et al* (180a) described a woman who developed a "fist size" lymphadenopathy in the right axilla One year later deep seated, "pea" sized cutaneous nodules appeared in the right scapulothoracic region which, within a few weeks, broke down and extended to form two large ulcers in the right anterior shoulder region These sharply outlined lesions, 10 cms and 4 5 cms , respectively, in size, were elevated and had a "pad-like margin with soft uneven bases which were covered with greenish fetid pus The first patient described by Shelmire (298) was a 54 year old man who had numerous "bean-sized' brownish cutaneous tumors on the neck and right half of the thorax, several of which were centrally ulcerated The histologic diagnosis, at autopsy, was Hodgkin's disease of the skin and lymph nodes His second patient was a 'middle aged" woman who had marked inguinal, axillary, cervical and supraclavicular lymphadenopathy and a "movable" tumor mass of "pigeon's egg size in the left breast The left axillary lymph nodes were from "pea to walnut" size with an adherent, inflamed overlying skin There was a 2 5 cm ulcer, which exuded a serous fluid, in the center of the inflamed area

This ulceration extended to involve the entire right axilla within the following three months The autopsy diagnosis was Hodgkin's disease of the lymph nodes and cutaneous ulcerated areas and the breast tumor showed granulation tissue with innumerable Sternberg-Reed cells

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A patient having cutaneous Hodgkin's disease with a terminal dissemination through the blood stream was reported by Bersack (27b) This 44 year old man first developed a 'lump" on the right calf which grew to 'hen's egg" size, became ulcerated and was followed by new ulcerated lesions The histopathologic picture of the older lesions revealed Hodgkin's dis

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ease The cutaneous nodule suddenly enlarged and a generalized eruption of "hundreds" of small, circumscribed, papular, nodular, erythematous lesions appeared, associated with chills, fever and stupor He died eight days later

An 18 year old boy who had Hodgkin's disease for one year was described by Kierland and Montgomery (170a) Cutaneous plaques, present on the left thorax for two months ulcerated within two weeks' time The ulcerated area consisted of confluent, slightly tender nodules, many of which had ulcerated The histologic diagnosis was Hodgkin's disease This patient had been previously presented by O Leary *et al* (247b)

The patient reported by Yamasaki (358) was a 42 year old woman who developed a "huge growth' on the right side of the neck where there was lymphadenopathy Similar lesions extended to the right shoulder and axilla and to the left supraclavicular region An ulcer, which resembled an "eroding sarcoma," developed on the right side of the neck and extended toward the nape A patient presented by Symmers (320 case 13) had cutaneous nodules with infiltration and destruction of the muscles and tendon sheaths of the right forearm Fuchs (111) reported a patient whose nose was a livid red color with a 'trumpet-like" swelling at the tip The bridge of the nose was destroyed and there were five nodular, "partly broken down partly bleeding,' tumor masses in the nasal passages Ulcerative cutaneous lesions occurring in patients with Hodgkin s disease were also described by Epstein and MacEachern (94) Cerutti (58), Durand *et al* (90), and Huguenin *et al* (156)

Case Report A 56 year old man who had specific ulcers of Hodgkin s disease from underlying lymph node involvement first developed a small painless nodule in the left inguinal region five months previously This caused obstruction and resulted in edema of the leg below the knee and the skin of the ankle assumed a mottled red color Four months later the right ankle became swollen and progressed to involve the entire leg with a massive pitting edema The skin of the leg was warm



37 Ulceration of the skin due to underlying lymph node involvement

erythematous, scaling and pruritic He had femoral and inguinal lymphadenopathy and there was edema and induration of the entire left femoral region Histologic examination of an inguinal lymph node revealed Hodgkin's disease The patient died nine months after onset of the disease and autopsy revealed Hodgkin's disease and pulmonary tuberculosis There was a deep-seated ulcer containing considerable purulent fluid in the left inguinal region The skin was scaly and atrophic while early lesions were present on the left thigh and lower leg The testicle was enlarged and the scrotum appeared red and indurated There was a large mass surrounding the aorta extending up to the diaphragm, partly surrounding the lumbar vertebrae and continuous with a large mass which almost completely filled the pelvic cavity This tumor surrounded the iliac vessels and infiltrated the psoas muscle The tumor, which weighed 2330 gms, was composed of smooth, soft, grey, slightly translucent tissue with small yellow necrotic areas

Case Report A 48 year old man had pulmonary tuberculosis, with laryngeal involvement 25 years previously but the disease was considered to be arrested after one years' hospitalization and had not recurred The first symptoms of Hodgkin's disease were a large fluctuant lymph node extending from the left clavicular to the mastoid process which had been present for one year There was complete disappearance of this swelling following roentgenotherapy However nine months after treatment progressive swelling and tenderness of the manubrium sternum medial heads of both clavicles and upper three or four ribs to their costal cartilages occurred There were numerous 0 5 cm nodules in these areas and the overlying skin was reddened with a tendency to small abscess formation On examination one year later he presented a deep seated ulcer at the upper end of the manubrium sternum This lesion 7 cms in size, was irregularly shaped and the edges showed a tendency to heal There was a 0 5 cm sinus opening, which contained pus, to the right of this lesion and another linear ulcer to the left of the larger ulceration A large tender, markedly painful area of matted indurated tissue involved the left axilla Autopsy revealed no evidence of pulmonary tuberculosis and the anatomical diagnosis was Hodgkin's disease Histologic examination

of the tumor nodules in the retroperitoneal region mesentery liver lungs and pancreas revealed an extremely active form of Hodgkin's disease There was a multiplicity of cell types including lymphocytes eosinophils and fine fibrosis

Diagnosis and Differential Diagnosis of Specific Cutaneous Lesions The cutaneous tumors occurring in Hodgkin's disease are usually of large size ulcerated and fungating While the diffuse infiltration of Hodgkin's disease is sometimes similar to that present in leukemia cutis universalis the process is never as extensive The tumors are usually bright red dusky purple or dark brown in color and usually occur on the trunk in Hodgkin's disease while leukemic tumors usually occur first on the head or extremities The tumors tend to run a more chronic course in Hodgkin's disease than in leukemia The ulcerative manifestations may present a variety of clinical pictures The initial extension and development is usually rapid after which they may remain stationary for some months as in the case described by Senear (294a) Gates (116) described the lesions as varying from "coin" to "palm sized" ulcers the larger ones usually few in number and the smaller ones very numerous The ulcers are usually sharply outlined are rounded or oval in shape although they may appear irregular serpiginous linear or "mangled" Although the border of the ulcer is usually elevated it may be undermined with a soft uneven base having a floor covered with granulation tissue or a purulent or necrotic material Palpation may elicit free bleeding and a fetid odor is usually apparent These ulcers may cause slight or severe radiating pain

According to Chevallier and Bernard (62) the tumors are irregularly distributed and are never generalized but predominate in the areas of the breasts back hips and shoulders They are sometimes isolated or grouped but rarely confluent and the adjoining tissues may be normal or diffusely infiltrated They stated that the tumors of Hodgkin's disease tend to ulcerate whereas those present in leukemia cutis do not have this tendency

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The patient reported by Arzt and Randak (10f) presented lesions covering most of the right parietal and occipital regions of the scalp which extended to the neck

Usually the border of the ulcer is sharply defined However the outline varies and may be round, as in the case described by Laederich *et al* (180a, b), irregular, as in Saalfeld's (285) case serpiginous, as reported by Nanta (239a) and Kren (178a), "mangled," as in Arzt and Randak's (10f) patient, or of a linear form, as described by Cole (64a) The margins are usually elevated and often have a "pad like" elevation, as in Gadrat's (114a) patient The margins may be undermined and flabby or sharply "punched out," resembling a gumma, as described by Bine (30), Alderson (6) and Kren (178a) The ulcers are usually deep with an uneven floor which is covered with abundant purulent or necrotic material or granulation tissue, and have a soft base while in most cases the exudate has a purulent odor The ulcers usually bleed freely when touched and there is usually pain of variable degree, which may at times be severe

Two of Chevallier and Bernard's (62) patients had scattered lesions They found that of 27 patients in whom the ulceration occurred as a single lesion or as multiple lesions in a restricted area, 21 had involvement of the submaxillary clavicular, axillary and thoracic regions

Lymph node and tissue imprints were first used by Nanta and Chatellier (239c) in the diagnosis of cutaneous Hodgkin's disease and have proved to be of great diagnostic value Sweitzer and Winer (319b) found that Sternberg Reed cells were much more typical in lymph node imprints than in tissue sections They described the lymph node imprint technic as follows "An excised or punched out, unfixed specimen is cut into two parts and compressed in a forceps The exuding surface is touched lightly on a clean glass slide The slide is then dried by rapid fanning for a few minutes and then stained immediately The staining technic is performed in the following manner according to Schleicher (291)

1) Apply 0 5 cc of Wright's blood stain (0 1 gm of stain in





38 Deep-seated ulcer over manubrium sternum

39 Same patient (illus 38) seven months later, following roentgenotherapy

formed by clumping of endothelial cells Sternberg Reed cells have a deeply staining nucleus with large nucleoli and coarse, irregular arrangement of the chromatin The proportion of the nucleus to the cytoplasm is that of a malignant cell

The ulcerated lesions of cutaneous Hodgkin's disease must be differentiated from syphilis, sarcoma, mycosis fungoides epithelioma, tuberculosis and leukemia The diagnostic difficulty in differentiating mycosis fungoides and Hodgkin's disease is mentioned frequently Mycosis fungoides is primarily a cutaneous disease whereas Hodgkin's disease is primarily a disease of the reticulum of the hemopoietic organs, namely, the lymph nodes spleen and liver Both diseases are granulomas and the clinical and pathologic differentiation, as mentioned by Senear (294a) and Lapiere (184a) are included under Mycosis Fungoides (Part I)

A patient described by Reimann *et al* (271) was believed to have relapsing febrile nodular panniculitis during life, but at autopsy the diagnosis of Hodgkin's disease was established

The differentiation from syphilis may be made on the results of serologic reactions and therapeutic tests The syphilitic ulcer usually does not have a purulent base, there is no tendency to hemorrhage and the adjacent lymph nodes are not enlarged according to Laederich *et al* (180b) Tuberculous ulcers are irregularly outlined with thin violaceous and undermined margins Although some lesions may greatly resemble epithelioma lymphogranulomatous ulcers rarely involve the face which is a frequent site of cutaneous carcinoma Leukemic cutaneous lesions rarely ulcerate and concomitant evidence of leukemia as well as the typical blood picture, will establish the diagnosis

5 *Mixed Form* Combinations of the various types of cutaneous lesions have been described Erythematous areas eczematous plaques infiltration and tumor formation are evidence that both nonspecific and specific cutaneous lesions may occur simultaneously

The 44 year old man reported by Arndt (9b) had cutaneous infiltrations and tumors which had appeared 15 to 20 years be-

60 cc of pure methyl alcohol) and allow to act on the imprints for two minutes,

2) Dilute the dye on the slide with 2 cc of distilled water (pH 6.4), mix well and allow to stain for ten minutes,

3) Wash off the diluted stain with distilled water and check differentiation under the microscope,

4) Differentiate by dipping the slide for one to three seconds in Schleicher decolorizer (distilled water 100 cc, pure methyl alcohol 5.0 cc, acetone 0.5 cc),

5) Rinse in distilled water and allow to dry in air."

Wilson (346) studied sections of skin and cutaneous touch smears in 176 cases representing 52 cutaneous diseases, in an attempt to evaluate the cutaneous smear as an aid in diagnosis. Results of the smears were interpreted as normal or nonspecific in 135 instances and as revealing the presence of neoplastic disease in 41 cases. Diagnosis in 15 of the latter cases was more specific than could be determined by study of histologic sections alone.

The essential histologic characteristic of Hodgkin's disease is the Sternberg-Reed giant cell which Sweitzer and Winer (319b) believed to be reticulum cells undergoing proliferation. They described this cell as one which contains a clear hydropic cytoplasm and has a large round, oval or lobulated nucleus which contains one or more clearly visible nucleoli. In acute forms of the disease, these cells present only a single dark nucleus, rich in chromatin or sometimes numerous cells in which the nucleus is undergoing mitosis. In the more chronic form of the disease, the cells are multinucleated, having undergone mitotic division of the nucleus. A polymorphism of the infiltrate which consists of lymphocytes, polymorphonuclear leukocytes, plasma cells, fibroblasts and eosinophils, as well as a tendency toward formation of fibrosis are also characteristic of Hodgkin's disease. Arndt (9b) and Bell (23) are among those who have stressed the polymorphism of the infiltrate, rather than the presence of Sternberg-Reed cells in the histologic diagnosis of Hodgkin's disease. The true Sternberg-Reed cells must be differentiated from pseudo giant cells which are

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fore the lymphadenopathy The cutaneous lesions consisted of more or less sharply bordered erythematous, scaly and thickened patches, widespread subcutaneous infiltration, not sharply differentiated, of soft consistency, and "palm" sized tumors with a flat or ulcerated surface which were pale brown or dark red in color and more prominent on the arms and trunk In the inguinal region, about the left breast, and on the inner side of the left arm, were "palm" sized areas of edematous swelling in the deeper layers of the skin and subcutaneous tissues These lesions varied in color from dark brown to purplish red The surface was thickened, resembling lichen simplex chronicus Because of the extremely long duration of the eruptions, its polymorphous appearance and particularly because of the development of tumors and nodules in areas which had been red, scaling and superficially infiltrated for many years, this case was considered to be mycosis fungoides However, histologic examination of the tumor revealed the correct diagnosis

Langley (183) described a 24 year old man who had lymphadenopathy and numerous subcutaneous and intracutaneous nodules on the right thoracic wall A mass, which appeared to arise from the bone at the left second chondrosternal junction, developed shortly after, grew to tangerine' size, and was firmly fixed to both the skin and bone A mass which appeared to arise from the lower cervical vertebrae developed a few weeks later There was a walnut' sized nodule at the right anterior axillary fold which became ulcerated and had a crateriform granulating hyperemic surface and a central yellowish slough The ulcer did not proliferate or fungate and appeared to be due to pressure rather than to active growth

Shelmire (298 case 3) described a middle aged woman who had marked inguinal cervical axillary and supraclavicular lymphadenopathy and a 'pigeon's egg' sized movable tumor in the left breast The left axillary lymph nodes were of "pea to walnut" size with inflammatory adherent overlying skin and a 2 5 cm ulceration in the center which exuded a serous fluid

During the following three months the left axillary lymphadenopathy extended to involve the entire axilla and a 2.5 cm slightly elevated bluish tumor mass appeared in the right axilla. Histologic examination of an isolated area of infiltration on the back several centimeters removed from the ulceration in the left axilla showed islands of lymphocytes often separated by bands of connective tissue fibrils in the middle and upper cutis. Deep in the cutis there was granulation tissue characteristic of Hodgkin's disease, a reticulum forming a mesh work which enclosed cells of different types: small and large lymphocytes, plasma cells, polymorphonuclear leukocytes, epitheloid cells and the uninuclear and multinuclear giant cells pathognomonic of Hodgkin's disease.

A patient reported by Lisa (1943) was a 56 year old man who complained of weight loss for six months while weakness and cutaneous nodules on the trunk had been present for three months. He had large fungoid like masses with ulcerated surfaces and innumerable subcutaneous masses of "pea to walnut" size scattered over the entire body including the scalp. Some of the lesions were slightly tender and some markedly hemorrhagic. There was a deep brownish grey pigmentation of the upper arms, forearms and legs and the skin was inelastic and extremely nodular, having a "cobblestone" appearance. He had moderate cervical and axillary lymphadenopathy, the nodes were discrete and not adherent to surrounding structures. Histologic examinations of the lymph nodes and cutaneous lesions were typical of Hodgkin's disease.

A 16

... gic reactions (Wassermann). Therefore antisyphilitic therapy was begun but he did not improve and the swelling of the temple was then incised and the pus evacuated. The body temperature remained elevated, the headaches became more severe and new swellings and suppuration appeared. Five month later there were an "immense number" of tumors and ulcers involving the entire body. The largest

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ulcerated verrucous and papular tumor involved the greater portion of the front half of the tongue There was a 3 by 2 cm irregularly shaped sharply demarcated ulcer with a granular base which simulated a gumma present on the right elbow The liver and spleen were slightly enlarged smooth on palpation and all the superficial lymph nodes were hard and enlarged from "pea to almond size He died of pulmonary edema five weeks after onset of symptoms Autopsy disclosed all the lymph node groups to be enlarged more marked on the left than on the right side and the nodes were soft and discrete There was nodular involvement of the cutaneous and subcutaneous tissues of the right arm and leg which was demonstrated to be tumor growth on histologic examination There were several nodular masses with ulcerative lesions on the face and lower lip one on the buccal side Numerous freely movable cutaneous nodules were present on the abdominal and chest wall but the ribs were apparently not affected There was extensive infiltration with tumor tissue connected with the skin on the scalp and forehead The dorsum of the tongue was covered with papillary growths from 0 5 to 1 5 cms in diameter which had indurated margins and occasionally necrotic centers Histologic study revealed that they were attached to the underlying tongue mucosa and muscles accompanied by induration of the normal tissue There were small nodular masses of tumor tissue present in the thyroid gland There was discrete cervical lymphadenopathy most marked on the left side and histologic examination revealed these nodes to be soft white and "evidently containing tumor masses"

A 22 year old woman reported by Konigstein (176) first presented small red cutaneous lesions below the right breast and a few enlarged lymph nodes The condition progressed rapidly and two years later only the skin of the palms and soles was unaffected At times the tumors became confluent and there was atrophy of the upper layers of the skin while in other areas the skin was infiltrated The tumors up to "walnut" size were purple or occasionally greyish green in color Post

was a round sharply demarcated lesion with abrupt margins which were the seat of infiltration involving the entire right temporal region This lesion extended down to the bone and the surrounding areas were swollen and painful The inguinal lymph nodes were of pigeon s egg" size and the axillary lymph nodes of pea size Hemogram revealed a marked reduction in hemoglobin and red blood cells with 58 000 white blood cells per cu mm and only 5 per cent lymphocytes The weakness and anemia increased and he died less than six months after onset of the disease

A patient having two irregularly shaped dollar sized freely movable raised infiltrated cutaneous lesions on the upper portion of the back and anterior aspect of the shoulder was presented by Rulison (283b) One dusky red lesion had an area of superficial ulceration while the other skin colored lesion was not ulcerated Histologic examination of the lesion from the back showed the usual cutaneous appendages a portion of which was replaced by an ulcer under which were the usual cellular elements lymphocytes fibroblasts and occasional small blood vessels However in the deeper layer and extending into the fat were areas of profuse granulomatous infiltration with Sternberg Reed cells innumerable lymphocytes and many polynuclear and multinuclear eosinophils The diagnosis was Hodgkins disease of the skin and lymph nodes A 56 year old man reported by Cannon (56a case 3) had pain and swelling of the extremities tender "lumps over the body and difficulty in urination for three months A diagnosis of metastatic carcinoma was made There were numerous *nodules involving the entire body including the face and scalp* The tumors from pea to walnut size were subcutaneous and intracutaneous Some of the freely movable skin colored subcutaneous nodules were hard while others had a dough like consistency Many cutaneous nodules were of a bluish color hard and movable The skin of all the extremities was of a bluish purple color markedly thickened and infiltrated with nodules A granulomatous fungating walnut sized ulcer was present on the left malar bone and a similarly sized red

to the tentative diagnosis of reticuloendotheliosis" However histologic studies at autopsy disclosed numerous Sternberg Reed cells in both the lymph nodes and the cutaneous lesions There was a marked proliferation of reticuloendothelial cells and some Sternberg Reed cells in the bone marrow Granulopoiesis was distinctly diminished Extramedullary hematopoiesis was not found in either the liver or spleen Von Buchem and Botman stated that from the "hypertrophic structure of the atypically swollen reticuloendothelium a decreased rather than a raised medullary function must be assumed" Since the post mortem histologic picture differed from the previous ones they believed that apparently the "initially found reticuloendotheliosis had been an indifferent primary stage of this acutely developing lymphadenoma"

6 Erythroderma Form Erythroderma may be specific or nonspecific in Hodgkins disease Although the specific form is not common such cases have been described by Arndt (9b) Konigstein (176) Tomlinson and Cameron (324) and Wirz (348) Patients having erythroderma in addition to cutaneous nodules have also been reported

Millers (224a) patient was a young man who presented a generalized nonspecific cutaneous eruption for three to four years before the development of lymphogranulomatous nodules The generalized erythematous eruption was pruritic consisting of fine bran like scales and ulceration over points of pressure This cutaneous picture together with lymphadenopathy and ultimate loss of hair and nails suggested the diagnosis of pityriasis rubra (Hebra) However the development of cutaneous nodules during the few months preceding death did not favor this diagnosis and Hodgkins disease was demonstrated histologically at autopsy A 54 year old man reported by Pohle and Clark (260) had developed "boils" 18 months previously which first involved the legs and thighs but soon spread to the arms and back He had a single firm palpable lymph node in the left cervical region There was a generalized scaly dermatitis which did not affect the hands or soles and several flat red to dark brown excoriated weeping areas

mortem histologic studies disclosed Sternberg Reed cells in many areas, including the skin, connective tissue and perito neum Hoffmann (153) described a 37 year old man who had multiple lymphadenopathy, most marked in the cervical region and edema of the right arm and neck There were numerous "bean to hen's" *egg sized bullae on the neck*, hands, arms, fingers, chest, back and legs which were "partly limp, partly tense" with serous or, occasionally, hemorrhagic contents Nikolsky's phenomenon was positive There were "knotty," "lentil to bean" sized, bluish cutaneous infiltrations on the neck The condition was thought to resemble epidermolysis bullosa but histologic examination of the lymph nodes and cutaneous tumors disclosed Sternberg-Reed cells

Von Buchem and Botman (332) reported a 31 year old woman who had developed a small red nodule near the right groin six weeks previously This lesion gradually increased in size and a few weeks later similar lesions appeared on the face Pyrexia developed and the cutaneous lesions spread over the body There was a bluish red, hard, circumscribed infiltration present in the right groin which extended up to the labia majora and down to 10 cms above the knee on the anterior aspect of the thigh There was a similar eruption of 'butter fly" shape involving the nose and cheeks Both areas of indura tion contained numerous "pea to bean" sized nodules of bluish violet to 'brick' red color There were similar sized yellow macules disseminated on the scalp and numerous 'brick" red to violet red nodules on the back There were occasional small, yellowish, flat, hard papules involving the forearms and legs Histologic examination of a cutaneous nodule revealed focal proliferation of reticuloendothelial cells around the subcutane ous capillaries Because of the proliferation of reticulum and swelling of the endothelial cells, a tentative diagnosis of "reti culoendotheliosis" was made Histologic study of a lymph node showed a striking proliferation of reticulum cells and a distinct polymorphism of the proliferated cells The large nuclei contained nucleoli and there were some eosinophil leukocytes between the reticular cells This picture also led

dale (205) A 56 year old man who had generalized Hodgkin's disease was reported by Leucutia and Price (188) He had marked swelling of both sides of the neck and face due to cervical submaxillary submental pre and post auricular lymphadenopathy as well as involvement of the parotid glands The appearance was that of a so-called "Mikulicz facies" This condition responded favorably to roentgenotherapy Acuna and Bonduela (2) reported a child who had Mikulicz's disease as a result of Hodgkin's disease

C Lymphogranulomatids

At times there is no definite distinction between toxic or nonspecific cutaneous lesions and true tumors or specific cutaneous lesions in leukemia or Hodgkin's disease The unity of these two conditions which frequently cannot be separated clinically or pathologically is often evidenced by the cases described in the literature The merging of these conditions may be almost imperceptible The connecting link between these two disease groups are the "ids" leukamids when associated with leukemia and lymphogranulomatids when associated with Hodgkin's disease Clinically they resemble nonspecific or toxic lesions but histologically they resemble specific or true cutaneous infiltration by either leukemia or Hodgkin's disease

Audry (11) designated all toxic eruptions as "ids" but in our opinion this grouping is incorrect This was well illustrated by Highman (149) who pointed out that the term syphilis designates a lesion due to the treponema pallidum and has the structure of the syphilitic infiltration When the term lepride is used the same significance is attached to the lesion so designated but with reference to Hansen's bacillus True Hodgkin's disease of the lymph nodes has a distinct histologic structure and a lymphogranulomatid should show the histologic picture typical of the disease This same premise is true for leukemia and the leukamids It is incorrect to group all toxic or nonspecific cutaneous lesions associated with Hodgkin's disease or leukemia as ids However if a "toxic" eruption also has a specific histologic picture of Hodgkin's disease or leukemia it

of infiltration from which several tumor masses, up to 5 cms in diameter arose The eruption was most marked on the flanks and the largest tumors were present on the right side of the forehead, back to the head and left arm and thigh

Van der Meiren (330 case 3) described a 20 year old man who had a generalized pruritic "eczema like" eruption which was progressive and resistant to treatment Thirty years later he developed tumors which simulated "mycosis fungoides" and responded favorably to roentgenotherapy However, ten years later the condition had become generalized and there were areas of lichenification on an "erythrodermic background" but there was no marked lymphadenopathy However, histologic examination of a cutaneous tumor revealed Hodgkin's disease Six years later (at the age of 66 years) he had become emaciated, cachectic and developed fever Hemogram revealed 2,200,000 red blood cells and 33 000 white blood cells per cu mm with 88 per cent neutrophils and 7 per cent eosinophils The skin showed a chronic erythroderma and the inguinal and axillary lymph nodes were markedly enlarged At autopsy, the mediastinal and prevertebral lymph nodes were markedly hypertrophic and old fibrous tubercular lesions were present in the lungs A 44 year old man who had a generalized pruritic eruption of 20 months duration was reported by Wile and Belote (343d) A generalized, patchy scaly erythroderma then developed which was associated with hyperpigmentation and superimposed lichenoid and annular papules in the patches He had axillary and epitrochlear lymphadenopathy and the inguinal lymph nodes were of "olive to egg" size Histologic examination of the lymph nodes and cutaneous lesions revealed Hodgkin's disease The blood eosinophilia was 28 per cent

7. ***Mikulicz's Disease.*** Mikulicz's disease is a symptom complex characterized by symmetrical swelling of the lacrimal orbital and salivary glands due to infiltration by small round cells

Although the occurrence of Mikulicz's disease associated with Hodgkin's disease is rare, such cases have been described by S L Ziegler (362), Minelli (226) and McDonald and War-

month old infant who first developed tiny petechial cutaneous hemorrhages The hemogram revealed anemia, a slight polynuclear leukocytosis, marked reduction of the blood platelets (88,000) and a diagnosis of thrombocytopenic purpura was considered There was also a tumor of the thymus gland and fever and the infant died six weeks after the cutaneous hemorrhages appeared Histologic examination of the skin revealed hemorrhagic nodules specific for Hodgkin's disease

Rothman and Spurr (281e) reported a 68 year old man who had diffuse, brownish grey, hyperpigmentation of the skin associated with pruritus The skin, which was moderately thickened and slightly lichenified in some areas, showed the specific histologic picture of Hodgkin's disease

A 38 year old woman, described by Rulison (283a) had symmetrical cutaneous lesions involving both cheeks, temples, parts of both ears and the postaural region This macular erythematous eruption was bluish red in color and occurred in diffuse, irregular patches which shaded off into the normal skin without a definite border It was difficult to determine infiltration because of the uniformity of the eruption, although it was probably present Lymphadenopathy developed two months after the cutaneous lesions appeared Histologic examination of the skin revealed nodules in the subepidermal tissue which had the same histologic picture as the lymph node

should be called a lymphogranulomatid or a leukamid and not a "toxic" eruption

A specific histologic picture of Hodgkin's disease has been found in some cases, with the following morphological lesions and are, therefore, true "ids" 1) Prurigo-like papules, 2) vesico-bullous lesions, 3) purpura, and 4) erythematomacular lesions

A 16 year old boy who had a nearly generalized papular eruption of eight years duration was reported by Sibley (300b) The semi-translucent, yellow-red, waxy papules resulted in a distinctly leonine facies but the lesions did not involve the sternal or interscapular regions A 65 year old woman, presented by Sweitzer (319a), had many small, discrete, elevated, markedly pruritic papules which first appeared on the neck and shoulders and later involved the greater portion of the body A nonspecific cutaneous eruption which had a specific histologic picture was described by Wile (343a) in a 24 year old woman who had prurigo like cutaneous nodules

A man with a prurigo-like papular cutaneous eruption, reported by Senear and Wien (294d), presented some nodules resembling the lesions of folliclis The eruption was considered to be nonspecific with a specific histologic picture Rulison's (283b) patient was a 59 year old man who had discrete maculo papular cutaneous lesions scattered over the legs and forearms Some lesions had indolent pustular centers while others showed denudation and oozing Numerous small punched-out scars, some pigmented, were present in the same areas These scars resembled those of papulo necrotic tuberculide This case also showed a specific histologic picture with nonspecific cutaneous lesions

A 19 year old woman, reported by Richter (273), had pruritus and a chronic papular urticaria perstans which had the histologic picture of Hodgkin's disease Bacher (13) described a 76 year old man who had a widespread petechial eruption which had the characteristic histologic structure of Hodgkin's disease

Wollstein and McLean (354) reported a four and one-half

ance of sleep was reported by Cornell (70) This 15 year old boy had a generalized papulonecrotic eruption with some urticarial lesions and pigmentation of the skin Among the 108 cases collected by C A Smith (309) two had toxic lesions simulating scabies and one had fine brownish macules with scaling borders which had been diagnosed as "fungous infection Craver (73b) reported toxic cutaneous lesions in eight or 13 per cent of the cases while jaundice occurred in 6 per cent and pruritus in 29 per cent

Among six patients having cutaneous lesions reported by Corbeille (67) three had pruritus two a generalized toxic eruption and one had scalp lesions The lesions varied in three patients one having had "blisters" and pustules involving the entire body including the palms and soles on two occasions Another had brownish circular lesions involving the entire body while the third had an erysipeloid eruption of the cheek and eye associated with pruritus redness and tenderness No specific cutaneous lesions were reported in this series of 33 cases

Andrews (8a) described a six year old boy who had bullous erythema Four months after the appearance of cervical lymphadenopathy an intense generalized pruritus most severe and persistent under the knees occurred A generalized erythematous eruption with circinate and gyrate lesions superimposed on the pruritus then appeared on the buttocks thighs and arms and displayed the various colors seen in erythema multiforme There were also numerous vesicular and pustular lesions about the right axilla and neck Involution was followed by depigmentation but the eruption recurred with bul[illegible]

[illegible] abrasions later crusted with a central vesicular pustule in some lesions There was a slight itching sensation and the hands particularly the fingers were "tumefied with the appearance of red macules and bullous lesions

Subcutaneous hemorrhages are not uncommon in children

VI.

CUTANEOUS LESIONS IN CHILDREN

Hodgkin's disease occurring in children has many similarities to Hodgkin's disease in adults, according to Craver (73b), and presents the same general clinical features and course, namely, lymphadenopathy, fever, puritus, cachexia and anemia. The sites of orgin appear to be similar in children and adults, usually occurring internally about the upper or lower respiratory or gastrointestinal tracts. Cervical, axillary or inguinal lymphadenopathy is usually a late symptom of an internal process present for some time.

Hodgkin's disease may occur at any age. The youngest patient recorded died at four and one-half months of age and was described by Priesel and Winkelbauer (264). The diagnosis of Hodgkin's disease was made by histologic examination of a lymph node removed from the mother one month before the infant's birth. Post mortem examination of the infant revealed Hodgkin's disease and it was presumed that the disease had been present at birth. Pinelli (258) reported a six month old infant who had Hodgkin's disease.

Hodgkin's disease appears to be more frequent in boys than in girls. Among 108 cases, C. A. Smith (309) found 81.5 per cent were boys and 18.5 per cent girls. The more common cutaneous lesions noted in children are the nonspecific type and consist of pruritus, papular eruptions and lichenifications from scratching. Lesions of this type have been reported by Feer (102), Wollstein and McLean (354) and Corbeille (67). A 13 year old girl who had an eczematoid eruption on the nose and cheeks was described by Abramowitz (1a). A patient having an intense generalized pruritus which caused disturb-

ince of sleep was reported by Cornell (70) This 15 year old boy had a generalized papulonecrotic eruption with some urticarial lesions and pigmentation of the skin Among the 108 cases collected by C A Smith (309) two had toxic lesions simulating scabies and one had fine brownish macules with scaling borders which had been diagnosed as "fungous infection Craver (73b) reported toxic cutaneous lesions in eight or 13 per cent of the cases while jaundice occurred in 6 per cent and pruritus in 29 per cent

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Subcutaneous hemorrhages are not *uncommon* in children

Such hemorrhages into the arms, hands and right foot of a five year old boy was described by Fischer (103) and a 17 year old boy who had petechial cutaneous hemorrhages was mentioned by Karsner (169) Hippel's (150) patient was a seven year old girl who had petechial and larger hemorrhages Acute fulminating Hodgkin's disease, characterized by pronounced toxemia, generalized lymphadenopathy, hepatosplenomegaly, jaundice and purpura, which proved fatal 15 days after onset, was reported by Newman and Pushkin (241) This patient was a 16 year old boy who, two weeks before this illness, was tattooed on the anterior aspect of the left forearm with resulting redness, swelling and tenderness for three days

Herpes zoster is not an infrequent toxic cutaneous lesion in children Pancoast and Pendergrass (250) reported two cases One (250 case 2) was a 10 year old girl and the other (250 case 3) a nine year old boy Lockwood *et al* (197) mentioned a 15 year old boy who had zoster A six year old boy, reported by Limper (192), developed herpes zoster, which brought attention to the lymphadenopathy, as the presenting symptom of Hodgkin's disease The zoster involved the tenth left intercostal nerve Four subcutaneous nodules on the anterior chest wall of the same side were found to be diagnostic of Hodgkin's disease Sibley's (300b) patient was a 16 year old boy who had an extensive papular eruption involving most of the trunk and extremities while the face had a definite leonine appearance Severe gangrenous zoster, preceded by neuralgic pain over the left lower ribs appeared and left deep scarring

Erythroderma occurring in a Negro boy was reported by Jones and Alden (166) The symptoms of an intense generalized pruritic eruption lymphadenopathy and loss of hair in a young person resulted in a clinical similarity to pityriasis rubra (Hebra) Two patients reported by Symmers (320) had exfoliative dermatitis One was a 20 year old boy and the other a 12 year old girl who also had jaundice Bruck (47) reported a 17 year old boy who had extensive erythroderma, many "walnut" sized tumors and striae atrophicae

It appears that toxic cutaneous lesions as well as specific cu

neous lesions occur somewhat less frequently in children than in adults having Hodgkin's disease There is a tendency o relative leukocytosis in children which may reduce the tendency to relative polynucleosis The presence of eosinophilia ppears to be more common in children

The occurrence of specific cutaneous lesions in children with Hodgkin's disease is rare In a series of 33 cases of children



40 Ulcerated lesion of Hodgkin's disease in a child

having Hodgkin's disease Corbeille (67) could find no evidence of specific cutaneous lesions There are however a few cases in the literature Nobl (245c) described a seven year old boy who had numerous tumor like infiltrations These tumors were most marked on the face causing almost complete closure of the eyes and a grotesque distortion of the features with the facial appearance "that of an octogenarian" Histologic examination of a tumor showed Hodgkin's disease Nodular lesions of the face resembling leonine facies was described by Cerutti (58)

Jordan *et al* (167) reported a 16 year old boy who had a swelling of the right temple The lesion was incised and the

pus evacuated but new swellings and suppuration occurred Five months later a generalized eruption consisting of numerous nodules and ulcers appeared The largest ulcer in the right temporal region extended down to the bone and was round and sharply demarcated with abrupt margins composed of hard infiltrations Autopsy revealed Hodgkin s disease Wrong (356) reported Hodgkin s disease of the scalp in a 12 year old boy A small firm nodule of hickory nut size had appeared in the left parietal region following trauma Histologic examination showed a striking similarity of the general structure and cellular picture to Hodgkin s granuloma However the subsequent history of well being and disappearance of the tumor following three small exposures of roentgen rays makes this diagnosis questionable

VII.

MUCOUS MEMBRANE LESIONS

INVOLVEMENT of the mucous membranes is rare, in contrast to the frequency of cutaneous involvement, in Hodgkin's disease and pigmentation of the mucous membranes of the mouth appears to be very infrequent Epstein and MacEachern (94) found stomatitis in only 0 6 per cent of their cases as compared to 12 12 per cent stomatitis in leukemic patients The types of oral lesions found in Hodgkin's disease are nodules, ulcers and bullous lesions which may be hemorrhagic or even necrotic in character These lesions are more frequent in acute leukemias and must be differentiated from thrush pemphigus, dermatitis medicamentosa and various granulomatous processes Jackson and Parker (159f) divided Hodgkin's disease into the paragranuloma granuloma and sarcoma types They stated that the tonsil and nasopharynx are rarely involved in Hodgkin's granuloma and only six of their 213 cases showed such involvement One patient had a large translucent mass in the posterior pharynx and the other five had unilateral involvement of a tonsil by a whitish or translucent mass with occasional ulceration of the surface This tonsil involvement occurred early in the disease in all cases and was invariably accompanied by notable cervical lymphadenopathy This fact illustrates the rapid development of this form of the disease In contrast, Jackson and Parker found that involvement of the tonsils and nasopharynx by Hodgkin s sarcoma is not rare, since it occurred in 11 per cent of their cases In three patients the tonsil was involved and in one the palate and antrum The initial symptoms found most frequently are localized pain nasal obstruction tumor in the throat and sore throat In the course of the disease there is invariably loss of weight and dyspnea some-

pus evacuated but new swellings and suppuration occurred Five months later a generalized eruption consisting of numerous nodules and ulcers appeared The largest ulcer, in the right temporal region, extended down to the bone and was round and sharply demarcated with abrupt margins composed of hard infiltrations Autopsy revealed Hodgkin's disease Wrong (356) reported Hodgkin's disease of the scalp in a 12 year old boy A small firm nodule of "hickory nut" size had appeared in the left parietal region following trauma Histologic examination showed a striking similarity of the general structure and cellular picture to Hodgkin's granuloma However, the subsequent history of well being and disappearance of the tumor following three small exposures of roentgen rays, makes this diagnosis questionable

tion of vesicles leaving red raw oozing surfaces The skin on other parts of the body was normal except for a striking pallor due to marked secondary anemia Histologic examination of the lesions on the prepuce revealed the epidermis to be edematous and separated from the corium by a serosanguinous exudate The corium particularly the subepidermal layer was densely infiltrated by cellular elements mostly mononuclear leukocytes epitheloid and endothelial cells Fibroblasts and reticular cells with scattered eosinophils which appeared distinctly related to extravasated blood were present in the masses No cells characteristic of Sternberg Reed cells were found A diagnosis of Hodgkin's disease was concurred by two histopathologists Superficial lymphadenopathy was present only in the chains draining the affected areas Deep roentgenotherapy administered to the chest, apparently also irradiated the jaws since there was complete regression of the oral lesions following decrease in the regional lymphadenopathy

Cornell (70) mentioned a patient who had lesions on the oral mucous membranes in addition to numerous specific cutaneous lesions Milian and Degos (223c) described Hodgkin's disease of the tongue but the diagnosis is to be questioned since

ulcer at the base of the tongue which showed the histologic structure of Hodgkin's disease The patient reported by Nanta and Chatellier (239c) developed a thickened lesion on the tongue three years before lymphadenopathy appeared Although the histologic picture of the tongue lesion was not conclusive the histologic study of a lymph node revealed Hodgkin's disease

Hodgkin's disease of the tonsil although extremely rare was described by Wullstein (357) and Bingold (31) Richter (273) reported a 43 year old woman who had marked ulceration of the left tonsil in addition to specific cutaneous nodules S I Ziegler (362) found the tonsils to be enlarged in three of

times due to nasal obstruction, is not infrequent The tumor is highly invasive and destructive and the life expectancy is very short, no patient in their series lived more than three years after onset of the disease The tumors of the tonsil are extremely large and ulcerated and while response to initial radiation therapy is good, the recurrence is rapid and subsequent irradiation has little effect

A patient described by Czezowska and Mierzecki (75) had a cutaneous eruption accompanied by lesions in the buccal and pharyngeal mucosa which resembled, but were less intense than, those on the skin The ulcerations disappeared following roentgenotherapy of the lymph nodes B Bloch (34) reported a woman who had generalized, recurrent "palm sized" erythematous plaques over which bullae and vesicles 0 5 to 2 5 cms in size, developed and bullous lesions appeared in the mouth from time to time Konigstein (176) reported a patient who had an eruption closely resembling pemphigus vulgaris in whom vesicles and bullae, in an annular or arc like arrangement, appeared in the mouth Lamb and Stout (181 case 3) described a 43 year old man with Hodgkin's disease who had gingivitis, stomatitis and a 'raw" tongue

Haeckel (135) observed nodules in the mucous membranes of the upper lip and Dutoit (91) noted nodules in the hard palate Bine (30) reported a woman who had cutaneous nodules which disappeared spontaneously within a week However, eight months later nodules appeared on the hard palate which broke down and ulcerated, one assuming a punched out character, suggestive of late syphilis There was a sloughing lesion which perforated 2 cms in size, on the opposite side of the palate

The patient described by Symmers (320 case 10) had vesicles on the buccal mucosa, lips and tongue as well as vesicles on the face Sharlit (296) reported a 52 year old man who had patchy infiltration of the membranous lining of the prepuce, glans penis, tongue lips and buccal mucosa Subsequent observation confirmed the opinion that denudation was preceded by a slow lifting of the epidermal layers, without forma-

VIII

ASSOCIATION WITH OTHER DISEASES

A Systemic Mycosis

1 Histoplasmosis. Histoplasmosis is a fungus disease which mainly involves the reticuloendothelial system According to Rothman (281b), the frequent association of lymphomatous diseases, particularly Hodgkin's disease, with deep mycotic infections has been recently noted, although the nature of such an association is not clear It would appear that the lymphoma was the primary disease in some cases J F Murray and Brandt (238) postulated the association of the two diseases as follows 1) coincidence, 2) malignant lymphoma predisposing to fungus infection, 3) development of a malignant reticulosis as a result of the fungus, and 4) a histologic reaction to the fungus that stimulates a malignant lymphoma

Two cases were described by Ende *et al* (93) In one, the histologic picture of a lymph node resembled typical tuberculosis superimposed on Hodgkin's disease, although the cultures produced a heavy growth of *Histoplasma Capsulatum*, rather than Koch bacillus

In a report of subclinical histoplasmosis of the appendix, Rafters (268) described two patients and a relative of a third who subsequently developed malignant reticulosis Hodgkin's disease was diagnosed on histologic examination of a lymph node two months before death in the patient reported by Bunnell and Furcolow (49) At autopsy, histologic studies revealed "changes consistent with Hodgkin's disease in the liver, spleen adrenals and lymph nodes" There were large numbers of parasites having the morphologic characteristics of *H Capsulatum* present within the lesions in the adrenal glands and

54 cases of Hodgkin's disease. Westphal (341) also noted this enlargement and believed it was frequently the starting point of the disease. Dutoit (91) described involvement of the tonsils in a patient who also had involvement of the eyelids. Jackson and Parker (159f) reported a 45 year old man who had a large sloughing tumor of the right tonsil which extended up into the nasopharynx. Autopsy revealed Hodgkin's sarcoma involving the right tonsil with direct extension to the nasopharynx and sphenoidal sinus and involvement of the pituitary gland, right orbit, right temporal bone and adjacent dura. A 40 year old man who had a small painless submaxillary tumor on the right side and moderate enlargement of the right tonsil was described by Martinez and Sierra (216). Milian *et al* (223d) described a man who had a painful ulceration of the left tonsillar region which deeply invaded the posterior portion of the soft palate. This ulceration, present for two years, had not been benefitted by tonsillectomy. There was immediate response to intensive roentgenotherapy but the growth recurred 15 days after treatment. A 37 year old Negress whose first symptom of Hodgkin's disease was swelling of the right tonsillar region was reported by Jaffe (161b). The fact that involvement of the tonsil is much more frequent in lymphosarcoma than in Hodgkin's disease is an important differential diagnostic point. Yates and Bunting (359) observed the histologic picture of Hodgkin's disease in tonsils which were not grossly affected.

Primary localization in the nasopharynx is also rare but has been described by Berendes (25) and others. Two patients who had Hodgkin's disease involving the oral pharynx and cervical lymph nodes following definite inflammatory lesions in the throat were described by Putschkowsky (266). The involved tonsils and cervical lymph nodes showed the histologic picture of Hodgkin's disease in both cases.

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J F Murray and Brandt (238 case 3) described a 13 year old boy who developed an enlarged lymph node in the left cervical region five years previously Four years after onset histologic examination revealed primary lymphocytic lymphoma (or reticulosis) Further studies disclosed numerous yeast like bodies of *H Capsulatum* He also developed an atopic dermatitis at this time The left cervical lymph nodes began to fluctuate and needle puncture produced pus in which abundant forms of Histoplasma were demonstrable

The only report of Hodgkin's disease complicated by histoplasmosis cryptococcosis and tuberculosis was that of Rodger *et al* (274)

2 *Cryptococcosis* In reviewing the reported cases of cryptococcosis Gendel *et al* (118) found an incidence of 8.5 per cent associated with Hodgkin's disease They found 13 cases of this association in the literature and described an additional case W Freeman and Weidman (109) first reported the coexistence of Hodgkin's disease and cryptococcosis in 1923 They described a 39 year old man in whom the histologic examination of an enlarged lymph node had revealed Hodgkin's disease five years previously The patient died of central nervous system cryptococcosis and autopsy disclosed enlargement of the spleen right axillary and mesenteric lymph nodes However the microscopic appearance was no longer considered to be typical of Hodgkin's disease A similar case reported by F B Smith and Crawford (310) was a 31 year old woman who developed a mass over the left scapula which was histologically suggestive of Hodgkin's disease This tumor disappeared following radiation therapy One year later she manifested central nervous system complications and died six months later At autopsy there was no evidence of the original scapular tumor and the brain spinal cord and chest showed cryptococcic infection There were lesions suggestive of Hodgkin's disease present in the posterior mediastinum

A 31 year old man who developed a swelling of the neck

liver Miller *et al* (224b), among others, noted histoplasmosis may simulate Hodgkin's disease histopathologically They described a 37 year old man who developed left cervical lymphadenopathy one year before the histologic diagnosis was made Five years after onset, he developed chills, fever, weight loss and abdominal pain and the following year a nodule, which became ulcerated, appeared in the center of the tongue The histologic examination and cultures of this lesion revealed *H Capsulatum* and this organism was later found in an axillary lymph node He died seven years after onset of the disease and autopsy *disclosed histoplasmosis of the tongue,* cervical and axillary lymph nodes, and Hodgkin's disease of the cervical lymph nodes, spleen and liver and disseminated miliary tuberculosis

The patient described by R J Parsons and Zarafonetis (254) was a 56 year old man who developed abdominal pain anorexia, vomiting, weight loss, dyspnea, lymphadenopathy and an abdominal mass Histologic examination of an inguinal lymph node revealed Hodgkin's disease and the hemogram showed a mild anemia severe terminal leukopenia and 5 to 7 per cent eosinophils He died a year after onset of the disease and autopsy disclosed the typical lesions of Hodgkin's disease involving the abdominal lymph nodes, spleen, liver and bone marrow, while lesions of histoplasmosis were present in the peripheral and visceral lymph nodes, lungs, liver, spleen and bone marrow The lesions were sometimes intermixed in the bone marrow These investigators stated "Did Hodgkin's disease, a disease in which cells of the reticuloendothelial system become malignant, predispose this man to histoplasmosis a disease which is characterized by parasitization of the cells of the reticuloendothelial system by the yeast like form of the fungus *H Capsulatum*?

This subject has been reviewed by Cawley and Curtis (57) They noted that the number of cases in which histoplasmosis and 'lymphoblastomas have been coexistent is greater than can be accounted for by mere chance and it appears, as previ

ously noted that there may be a relationship between these diseases"

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A 31 year old *man who developed a swelling of the neck*

which proved to be Hodgkin's disease on histologic examination was reported (54b) The lymphadenopathy receded following radiation therapy but a year later, following trauma to his head, headache and neck stiffness developed The cervical lymphadenopathy recurred, the spleen became palpable and cryptococci were found in the spinal fluid Autopsy revealed a cryptococcic meningitis with concomitant involvement of the kidney, adrenal glands and lungs The spleen and bronchial and retroperitoneal lymph nodes showed Hodgkin's disease An 18 year old Negro who had axillary, cervical and inguinal lymphadenopathy for three years was described by Fitchett and Weidman (104) Three months before death he developed headache and signs of central nervous system involvement At autopsy, disseminated cryptococcal involvement was found The enlarged spleen contained cryptococci and the histologic picture was suggestive of Hodgkin's disease They considered the possibility that the *C Neoformans* might be one of the several organisms which may induce the histologic picture of Hodgkin's disease Another case of Hodgkin's disease having this complication was reported by Burger and Morton (50b) who also believed that this infection could produce granulomas closely simulating Hodgkin's disease The patient reported by Cox and Tolhurst (72) was admitted in a moribund condition and the diagnosis of both Hodgkin's disease and cryptococcal infection was made only at autopsy

Gendel *et al* (118) described a 39 year old man who first developed right axillary lymphadenopathy and subsequently cervical and inguinal lymphadenopathy Three years after onset, histologic examination of a cervical lymph node and a cutaneous lesion revealed Hodgkin's disease One year later he developed headache and culture of the spinal fluid was positive for *C Neoformans* Autopsy disclosed crytococcosis involving the brain, meninges, lung, spleen, intestines, subclavian abdominal and hilar lymph nodes These investigators found that in 13 of the reported cases the diagnosis of Hodgkin's disease was made prior to the diagnosis of cryptococcosis Ten patients were given roentgenotherapy which caused regression

of the swelling and symptomatic remission in all cases This association of two uncommon diseases is too frequent to be regarded as a matter of chance, according to Gendel *et al* (118) Some investigators believe that cryptococcic infection might occasionally produce a tissue reaction similar to that in Hodgkin's disease Numerous microorganisms have been isolated in Hodgkin's disease, the most frequently mentioned include diphtheroids, avian tubercle bacilli and brucella Because of the frequency of infections in patients having Hodgkin's disease, Desjardins (80a) suggested that any chronic infection was the factor immediately responsible for malignant hyperplasia of the lymphoid structures This viewpoint would indicate that Hodgkin's disease is a syndrome produced by a variety of infectious agents, including *C Neoformans* The alternative explanation for the association of these diseases would be that patients having Hodgkin's disease are prone to develop various infections The poor immunologic responses of these patients was mentioned by Dubin (86) and by Rostenberg and Bluefarb (279a, b), who believed this could explain their failure to react to tuberculin, the decreased incidence of positive serologic reactions for syphilis and their tendency to develop infections Benham (24) has shown that cryptococci can be present in normal skin and that these organisms are

[illegible] patients having Hodgkin's disease would permit their own cryptococci to "gain a foothold and produce clinical disease"

Four cases of coincident lymphoma and cryptococcal infec- [illegible]

un- [illegible]

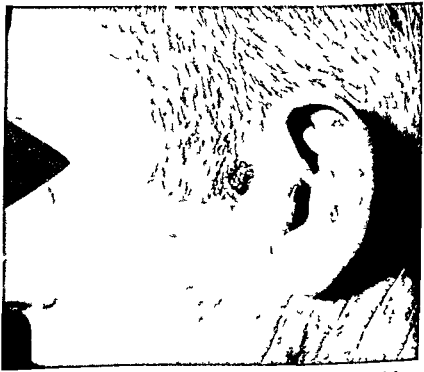
[illegible] association of paracoccidioidal granuloma (or South [illegible]

[illegible] generalized trichophyton rubrum infection and lymphoma

B Carcinoma

The coexistence of carcinoma and Hodgkin's disease is not common. The coexistence of multiple primary carcinoma is rare but is more frequent than is Hodgkin's disease associated with other neoplastic processes according to Skapier and Friedman (305). They did not believe that Hodgkin's disease is inhibitory to the development of carcinoma however since Hodgkin's disease usually affects younger age groups which may explain this infrequency. The short duration of Hodgkin's disease may also explain the infrequency of this association.

A 28 year old woman having Hodgkin's disease of the ipsolateral axillary lymph nodes and carcinoma of the breast was described by Craver and Sunderland (73f). Both conditions were proved histopathologically. Skapier and Friedman (305)



41 Basal cell carcinoma of the face in a patient with Hodgkin's disease

reported two patients who had Hodgkin's disease and mammary carcinoma

The patient described by Lapiere *et al* (184b) had Hodgkins disease and carcinoma of the stomach A 53 year old woman who died from perforation of the large intestine was reported by Craver and Sunderland (73f) Autopsy revealed Hodgkin's disease of the right submaxillary region and adeno carcinoma of the colon

A 65 year old man who had Hodgkin's disease and a squamous cell epidermoid carcinoma, grade 1, in the right sub maxillary region was reported by Fraser (107b) The man described by Torrey (325) had Hodgkin's disease as well as squamous cell carcinoma of the neck and verrucae acuminata involving the entire genital and anal regions We have observed a patient with Hodgkin's disease and a basal cell carcinoma of the face

C Tuberculosis

The association of Hodgkin's disease and tuberculosis is well known and has been described by numerous investigators including Miller *et al* (224b) and Rodger *et al* (274)

IX.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

THE DIAGNOSIS of Hodgkin's disease is dependent upon the cytopathologic appearance of the diseased tissue Differentiation is usually possible by histopathologic examination Other diseases to be considered in the differential diagnosis of Hodgkin's disease include granulocytic and lymphocytic leukemia, reticulum cell sarcoma, giant follicular lymphoblastoma, Boeck's sarcoid, nonspecific inflammatory lymphadenopathy, certain fungus diseases, lymphopathia inguinale, typhoid fever, brucellosis, tuberculosis, syphilis and infectious mononucleosis

Lymphosarcoma. The differential diagnosis between Hodgkin's disease and lymphosarcoma is frequently difficult Several cases of Hodgkin's disease which were diagnosed as lymphosarcoma have been described and some investigators were of the opinion that there was a definite transformation of Hodgkin's disease to lymphosarcoma However, others were of the opinion that lymphosarcoma had been engrafted on the inflammatory tissue of Hodgkin's disease Sweitzer and Winer (319b) believed that an occasional mitotic figure in proliferating reticulum suggests an acute, rapidly fatal type of Hodgkin's disease Numerous mitotic figures and a more monomorphous infiltrate suggests lymphosarcoma

Leukemia Both Hodgkin's disease and leukemia may be characterized clinically by lymphadenopathy Acute leukemia may be accompanied by severe purpura while in chronic leukemia there may be cutaneous nodules similar to those present in Hodgkin's disease and, as a rule, leukemic tumors do not ulcerate The peripheral blood picture is usually diagnostic in leukemia and the histologic examination will reveal uni-

form monomorphous cell tumors rather than the proliferation of connective tissue observed in Hodgkin's disease The histologic differentiation of monocytic leukemia is based on differentiation of the histiocyte from the Sternberg Reed cell The histiocyte presents phagocytosing properties and an extremely irregular cytoplasm while the Sternberg-Reed cell has no phagocytosing properties The preponderance of monocytes in the peripheral blood is also characteristic of monocytic leukemia

X.

PROGNOSIS

THE EXTENT of the disease at the time treatment is instituted is the most accurate indication of the life expectancy in Hodgkin's disease, according to Nice and Stenstrom (242) Survival figures correlate more closely with the clinical stage of the disease than with the histologic picture, or any other factor They listed the stages of development as 1) Involvement of a single group of lymph nodes or a single lesion elsewhere in the body, with no constitutional symptoms, 2) involvement of at least two proximal regions of lymph nodes of either the upper or lower trunk, with or without constitutional symptoms, and 3) involvement of multiple groups of lymph nodes, with or without symptoms, or the acute form of the disease without lymphatic involvement In a study of 208 cases of Hodgkin's disease, they found the 10 year survival rate to be 77 per cent for patients with stage one of the disease, 35 per cent for stage two, and 2 per cent for stage three

In a study of 1,000 proved cases of Hodgkin's disease with short and long survival periods, Finkbeiner *et al* (101) found that clinically detectable factors such as age, sex, race, color, marital status, family or personal history, extent of the disease, symptoms, presenting physical examination and laboratory studies were not reliable prognostic signs They stated that in spite of such unfavorable signs as generalized disease, constitutional symptoms, Hodgkin's sarcoma, or abnormal blood picture, carefully planned persistent therapy might result in pro longed survivals

Although there are reports of patients who remained in fairly good health for 12 to 14 years, many died within a matter of weeks Women appear to have a better prognosis than men

About 50 per cent of these patients died during the toxic stage associated with multiple visceral invasion or of terminal disease associated with secondary infection while many died of bone marrow exhaustion and aplasia Although deaths have been ascribed to the secondary effects of radiation improved radiotherapeutic technics and more careful laboratory studies have reduced this mortality rate Hoster and Dratman (154c) listed the factors associated with a good prognosis as a normal erythrocyte count a nearly normal sedimentation rate localization of the disease in one area definite superficial lymphadenopathy prior to therapy gain in body weight and the absence of leukocytosis or leukopenia The indications of a poor prognosis they listed as splenomegaly initial pyrexia marked pruritus pulmonary involvement predominant localization in the abdominal cavity gastrointestinal symptoms steady decrease in erythrocytes marked leukopenia, pronounced loss of body weight and increased sedimentation rate occurring early in the disease

Jackson and Parker (159c) believed that the prognosis can be correlated with the histologic picture of the involved lymph nodes They stated that "In broad terms Hodgkin's paragranuloma is a comparatively benign condition, occasionally progressing to Hodgkin's granuloma Hodgkin's granuloma is characterized by the most protean manifestations is usually though by no means invariably fatal within a few years and on rare occasions progresses to Hodgkin's sarcoma Hodgkin's sarcoma behaves as a highly malignant comparatively localized tumor rapidly resulting in death"

However L B Goldman and Victor (124b) and Mills and Pritchard (225) could find no relationship between the histologic picture of the lesions and the prognosis of the disease No histopathologic classification is possible since the lymph nodes in all stages of pathologic development may be present simultaneously in the same patient according to Slaughter and Craver (307) They found that of 14 cases diagnosed as Hodgkin's sarcoma" five survived for more than three years

and they believed the prognostic factors to be dependent upon the location and extent of the lesions

It is not possible to determine from the cutaneous picture whether the course of the disease will be severe or mild The first cutaneous changes occurred in Dujardin and Van der Meiren's (88) patient at the age of 20 years and he lived to 65 years of age The cutaneous tumors appeared only five weeks before death in Rusch's (284) patient

Shimkin (299) analyzed the mortality rate from Hodgkin's disease in the United States during the period 1921 through 1951 with respect to race, sex, age and distribution The findings were compared with those reported for leukemia The recorded mortality from Hodgkin's disease rose from 6 9 in 1921 to 17 0 per million in 1951 During this period the mortality from leukemia rose from 14 to 61 per million persons He found the mortality for men to be higher than for women in both diseases The predominance of men was more marked in Hodgkin's disease than in leukemia The incidence was higher among those of the white than the non white races in both diseases, the white predominance being more marked in leukemia than in Hodgkin's disease There was no peak rate during childhood in Hodgkin's disease as there is in leukemia and the increased incidence with age is much less marked in Hodgkin's disease than in leukemia The mean age at death for Hodgkin's disease and leukemia, for adults, increased by 3 5 and 8 0 years respectively, between 1925 and 1950 The male female sex ratio for Hodgkin's disease decreased slightly but there was a slight increase for leukemia during this period

In a recent study, Smetana and Cohen (308) stated that the correct diagnosis of the types of Hodgkin's disease and the differentiation of secondary histologic characteristics are of importance in the evaluation of the prognosis and for the choice of treatment They reviewed the records of 437 men between the ages of 17 and 58 years who were treated for Hodgkin's disease in Army hospitals during the second World War Histopathologic specimens, generally obtained by biopsy, were studied in 388 cases The differentiation by histologic type

revealed Hodgkin's granuloma in 308 cases (79 per cent), Hodgkin's paragranuloma in 35 (9 per cent), an unspecified group in 40 (10 per cent) in which a decision as to one type could not be made, and sarcoma in five (1 per cent). Of the 308 patients having Hodgkin's granuloma, 57 (18.5 per cent) showed secondary microscopic characteristics of sclerosis and 13 (4.2 per cent) showed those of sarcoid. Follow up was carried out by established methods which resulted in virtually complete tracing. The mortality rate among the 388 patients with confirmed Hodgkin's disease was 77.1 per cent at seven years after the diagnosis had been made, it was 28.6 per cent among the patients having Hodgkin's paragranuloma and 82.8 per cent among those with Hodgkin's granuloma. The difference in mortality between these types was significant. The seven year mortality rate among the patients with granuloma, without qualifying histologic characteristics, was 85.7 per cent, and among those with a sarcoid component it was 81.8 per cent. The difference in mortality between nonsclerosing and sclerosing Hodgkin's granuloma was 87.5 per cent as against 74.5 per cent and was of borderline significance. On reevaluation of the cases of 15 patients in whom a diagnosis of Hodgkin's paragranuloma had been made and who died it appeared from the original histologic "slide" that the diagnosis probably should have been Hodgkin's granuloma in five cases and "malignant lymphoma type uncertain" in one case. In the remaining nine cases the histologic diagnosis of paragranuloma made from study of the microscopic sections was confirmed. There were autopsy specimens in three of the 15 cases, two showed widespread Hodgkin's granuloma and one a generalized malignant

the cases

XI.

TREATMENT

A. General Discussion

There does not appear to be any permanently satisfactory therapy for Hodgkin's disease Even under the most favorable circumstances, permanent "cures" have never been attained However, adequate treatment may result in a prolonged useful life for many years Treatment should consist of continuous and adequate general supportive therapy including a high caloric and high vitamin diet, heliotherapy, fresh air, rest, relaxation, removal of known foci of infection and avoidance of upper respiratory tract infections, according to Hoster and Dratman (154c) Exposure to sun or ultraviolet light may aid in combating leukopenia, according to Heacock (140) and many patients feel in better health when they have a limited amount of physical outdoor exercise, Jackson (159b) stated Gilbert (120) found that patients who reside in rural areas appeared to tolerate the disease better than those in urban areas The maintenance of morale and the correction of mental depression is of great importance, according to Jackson and Parker (159e)

The importance of morale was also emphasized by Meyer (219b) who stated 'Of real importance is the maintenance over the years of the morale of these patients with malignant disease, this is an essential part of the physician's job One should never use the term Hodgkin's disease in the patient's presence but should substitute lymphogranulomatosis, for the layman either has read too much about the ravages of this disease in the newspapers or he has had a friend or acquaintance who has died of Hodgkin's disease A sincere, cheerful, optimistic attitude in dealing with these individuals and their families is of inestimable value These patients should be

allowed to carry on normal activity if desired since there is no evidence that normal activity is detrimental and I allow them much freedom Rarely is there an emergency to deal with and once the diagnosis is established by biopsy there is no occasion for excitement and panic that will be quickly transmitted to the patient Calm judicious planning of the therapy for the treatment of the symptoms since we do not anticipate cure is in order and at the onset for most patients roentgen therapy is the present treatment of choice However the newer therapeutic agents have been efficacious and worth while They have made the treatment of this disease more interesting requiring greater skill and judgement than when only roentgen therapy was available they have also permitted a more comfortable economically sound life and I believe an actual prolongation of life in many instances A totally pessimistic outlook is undesirable when dealing with the individual with Hodgkin's disease Life may be long and in rare instances there may be apparent cure Thus one can look to the future with anticipation that still more effective therapy will be developed for the treatment of Hodgkin's disease and one can derive some small satisfaction from the fact that the plight of if not the prognosis for such patients has already been ameliorated"

Roentgenotherapy appears to be the method of choice for the treatment of localized lesions while roentgen irradiation of selected specific areas together with nitrogen mustard appears to be the most effective therapy for disseminated lesions (92) The problem of therapy varies with each patient and there is a difference of opinion among radiologists as to the most satisfactory method of treatment *The effectiveness* of early thorough persistent roentgenotherapy has often been demonstrated However this *therapy must be used* with great caution to avoid possible renal insufficiency active tuberculosis in irradiated areas the development of *acute* Hodgkin's disease toxic depression of bone *marrow* or the deleterious effects of previous irradiation *Nitrogen mustards* appear to have the same effect as roentgenotherapy and appear to be of great



42 Mediastinal tumor of Hodgkin's disease

43 Same patient (illus 42) two months later, following roentgenotherapy

alue when roentgen rays are no longer effective The results with intravenous radioactive phosphorus have been disap pointing Surgery or roentgenotherapy may be necessary to relieve pressure symptoms or for prompt removal of the spinal



44 Collateral circulation present in a mediastinal tumor

cord block in paraplegia Surgical removal of accessible lymph nodes involved by Hodgkin's disease is reported to give favorable results Numerous chemotherapeutic agents have been used but the results of sulfonamide, vaccine and other biological therapy have not been favorable

Craver (73d) believed that Hodgkin's disease should be classified at the onset as 1) patients having the early and strictly localized form of the disease, 2) those presenting spread of the disease with relatively regional localization, and 3) generalized Hodgkin's disease He stated that in the first type "aggressive local attack is justified and that it would be defeatist policy to do as is advocated in some quarters, that is, to leave the early case untreated awaiting the onset of troublesome symptoms or, on the other hand, to give only the minimal treatment to the early case that would suffice to produce a regression" He also found that fairly aggressive attack upon the second group may produce long control of the disease Only in the generalized type does he believe that treatment should be comparable to that of leukemia, that is, the use of whatever agent, either general or local, which "will produce the best palliation for the longest possible time, a principle that has as its corollary the avoidance of over aggressive treatment" Craver stated that there are only three direct methods of attack upon Hodgkin's disease surgery, radiation and chemotherapy Surgery may be attempted to "cure' certain selected cases in which the process is strictly localized or it may be used in cases of bleeding gastric lesions or to remove residual accessible masses which have become radio resistant Radiation therapy is now practically limited to some form of roentgen ray therapy, and chemotherapy usually consists of nitrogen mustard or triethylenemelamine (TEM) Craver concluded that all other methods may be considered as adjuvants

C A Hall and Olson (136), who reviewed the therapy of malignant lymphoma stated that there is no conclusive evidence that localized Hodgkin's disease can be cured Although there is no question that therapy results in symptomatic improvement, they found that no conclusions as to the preferable

technics of roentgenotherapy can be made from existing data They believed that the combinations of nitrogen mustard and roentgen rays are more efficient therapy although the survival rate is the same when roentgenotherapy alone is used The survival rate for patients receiving TEM therapy has not yet been evaluated they found and some symptomatic relief is frequently obtained with steroid therapy in certain cases They were of the opinion that definite conclusions cannot now be drawn with regard to therapy partly because of "non standardized and inadequate methods of study The establishment of basic principles of method of study and better organization of effort would increase the value of future studies" They described the results of treatment with roentgen rays nitrogen mustard and surgery in 65 cases of Hodgkin s disease There appeared to be little difference "in the effectiveness of nitrogen mustard used as the sole or primary therapy when compared with the effectiveness of roentgenotherapy in producing and maintaining remissions"

B Roentgenotherapy

Roentgen ray irradiation appears to be the treatment of choice for localized Hodgkin s disease The more advanced and widespread type of the disease may not respond as effectively to roentgen radiation alone In the disseminated type the combination of nitrogen mustard and roentgen rays appears to be the most effective therapy

Pusey (265a) a dermatologist was the first to treat Hodgkin s disease with roentgen radiation This patient was a four year old boy who had cervical lymphadenopathy There was regression of the lymphadenopathy following irradiation and his general health improved However there was recurrence a short time later and the patient died following surgical removal of the involved lymph nodes Two years later Pusey and Caldwell (265d) stated that although the permanent results of this therapy could not be evaluated at such an early date they were convinced of the beneficial effects of roentgenotherapy for this disease since it appeared that useful life could

cord block in paraplegia Surgical removal of accessible lymph nodes involved by Hodgkin's disease is reported to give favorable results Numerous chemotherapeutic agents have been used but the results of sulfonamide, vaccine and other biological therapy have not been favorable

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much ill effect the results may be even further improved. A dose of more than 1 000 tissue roentgens is given in almost all cases and the dose in some may be as high as 2 000 tissue roentgens but rarely exceeds this amount according to Merner and Stenstrom. For treatment of cervical lymph nodes 900 roentgens in air is given to each of three fields including the anterior posterior and lateral field. Treatment of the mediastinum consists of 1 200 to 1 500 roentgens in air to each anterior and posterior field. Very large masses of long standing are usually more resistant to radiation than smaller more recently enlarged nodes and should be treated more heavily. The recently enlarged nodes should however be given a certain minimum dosage even though they may respond and return to normal size before the intended amount is given. It is impossible to predict the site of future involvement. Isolated areas may become involved such as the scalp or extremities while the large chains of nodes are not affected. Therefore they believed that prophylactic irradiation is contraindicated. The most favorable cases are those in which only one chain of nodes is involved and thorough irradiation is given after histologic diagnosis has been established. Some cases with generalized manifestations particularly pruritus fever and weakness show a marked response after treatment of the local lesions. The pruritus often clears rapidly and the patient's general condition is usually improved as the local areas respond. A 200 or 220 KV and ½ mm Cu + 1 mm Al filter were used for the peripheral lesions by Merner and Stenstrom. The half value layer was 9 or 1.3 Cu respectively. For the deeper lesions the filter was increased to 1 mm Cu + 1 mm Al the half value layers being 1.4 or 1.7. The results suggested that Hodgkin's disease may begin as a localized process which if arrested might delay the development of a generalized disease. It is reasonable to suppose that heavy roentgen ray dosage would produce as effective a result as surgery in the case of radiosensitive lesions such as lymphomas according to Merner and Stenstrom. In most cases roentgen ray therapy would be

be prolonged with long continued treatment Shortly after this report, Senn (295) described a case of splenomedullary leukemia which was successfully treated with roentgen irradiation

Following the original report of Pusey (265a, b, c) and Heineke (142a, b), the exceeding radiosensitiveness of both pathologic and normal tissues has become well known This fact has been utilized at times to determine whether a given tumor, by its early response to a given dosage, is of lymphatic origin, as mentioned by Blankenhorn (32) and Evans and Leucutia (96) Before the occurrence of extensive fibrosis, the radio-therapeutic test can be of great value in causing rapid and marked diminution, or disappearance of subjective and objective symptoms of Hodgkin's disease, according to Ginsburg (121a)

A comprehensive review of this therapy was done by Merner and Stenstrom (218) They stated that Hodgkin's disease is so varied in its manifestations that it is necessary to treat each case individually Different parts of the body should be treated in different ways, depending upon the accessibility of the involved nodes Advanced stages also require some modification A few basic principles are followed, however, in all cases Usually more than one lymph node in a chain is involved, this report continues and the whole group should be treated as a unit If the cervical nodes are involved on one side it appears advisable to include the supraclavicular and submaxillary nodes in one field The mediastinum should also be treated as a whole, rather than only the area containing a visible mass Usually the enlarged lymph nodes begin to respond within a few days after the first treatment and may disappear after a relatively small dose However some of the abnormal cellular structure indicating activity probably still remains in the nodes and local recurrence soon occurs Recurrences appear to be more radio-resistant and it is advisable to give a heavier dosage during the initial series to prevent these recurrences The series should be given in a relatively short time to produce the maximum effect and 14 days has been arbitrarily chosen as the upper limit If it can be given in a shorter time, without too

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general deterioration and died but nitrogen mustard therapy has now proved to be of value in some of these cases according to Lamarzi However an occasional patient may again become sensitive to roentgenotherapy following nitrogen mustard therapy

In the series reported by C A Hall and Olson (136), 31 patients were given roentgenotherapy alone An additional 17 patients received roentgenotherapy as the major part of their treatment but were later given nitrogen mustard Of these 48 cases the survival and total remission ranged from 0 to 125 + months 62 per cent survived for one year 39 per cent for two years 35 per cent for three years and 18 per cent for five years while 29 per cent did not respond sufficiently to therapy to be classed as a remission They noted a great variation in the individual response to therapy as some patients had remissions up to 93 + months while others who showed good initial response had progressively shorter remissions with subsequent therapy

Total Body Irradiation Small doses of roentgen irradiation to the entire body (spray irradiation) was described by Dessauer (81) in 1907 Chaoul and Lange (59) later reported 12 patients treated by this method who showed varying degrees of improvement

In 1931 Heublein (147) introduced a similar method of treatment which is known as the "Heublein Method" Moderate radiation of the entire human body would cause extremely

... low in-
tensity roentgen rays at a long target skin distance The dosage administered was approximately 17 r a day given at 0 86 r an hour for an average dose of 100 r

Medinger and Craver (217) treated 94 patients having Hodgkin's disease with the Heublein method *of irradiation* However no patient was treated by this method alone and additional local therapy was administered to each group of lymph nodes They found the average *survival rate to be* 42

more effective since all the nodes in the chain would be included according to Werner and Stenstrom

Nice and Stenstrom (242) advocated the use of intensive irradiation either alone or immediately after surgical excision in cases having a single group of lymph nodes or a single lesion elsewhere and no constitutional symptoms They also believed intensive irradiation is the best treatment for cases having involvement of at least two proximal lymph node regions of either the upper or lower trunk with or without constitutional symptoms Treatment with at least 2 000 tissue roentgens within a 14 day period is suggested The entire lymphatic chain should be irradiated in the event of involvement of any node Prophylactic irradiation should not be administered to possible future disease sites in order to assure adequate dosage tolerance in the diseased regions Nice and Stenstrom suggested that less intense therapy be given in cases having involvement of multiple groups of lymph nodes or when the disease is acute but without obvious lymphatic involvement Spray irradiation is occasionally used in cases of widespread involvement In cases of massive mediastinal lymphadenopathy small doses of 50 to 75 r in air are given initially to prevent edematous compression of the tracheobronchial tree They stated that laminectomy and subsequent roentgenotherapy should be administered immediately to patients who develop paresis from spinal cord compression

Treatment of five patients having involvement of only one chain of lymph nodes were reported by Slaughter and Craver (307) They had very successful results with local resection followed by irradiation therapy

Lamarzi (191a) was also of the opinion that roentgenotherapy is the treatment of choice for localized lesions in Hodgkin s disease The usual duration of Hodgkin s disease is three to five years when well managed by irradiation he stated However the course is shorter in some patients while others may live for ten or more years Eventually radiation will fail to cause regression of the lymph nodes and improvement in the general health Formerly these patients showed

tion' theory of their action in cells It has also been shown that solutions of casein exposed to mustard gas becomes ineffective in supporting growth though they are not harmful when fed to animals Apparently the mustard compounds cause intramolecular changes in proteins, and their residues, attached to amino acids like histidine, lysine and methionine, are not capable of being split off in the body The mustard compounds are especially useful when the disease is so widespread that it is impossible to treat it effectively with roentgen therapy Certain cases of Hodgkin's disease show negligible response to the drug, most of these patients are said to be radio resistant as well Large masses, invasive lesions, and foci in the skin and bone are said to be refractory to the [illegible]

either generalized or localized, are resistant to roentgen irradiation, and in patients having generalized symptoms (fever, pruritus, neurologic manifestations), who do not respond to other chemotherapy, according to Lamarzi (191a) and Kierland *et al* (170b) The latter investigators treated six patients having mycosis fungoides with nitrogen mustard In four patients the condition had been resistant to roentgenotherapy *It was their* opinion that nitrogen mustard is an adjuvant to previously recognized therapeutic measures and is of particular value when roentgenotherapy is of no benefit.

The mustard compounds appear to have a similar action and effectiveness in the treatment of Hodgkin's disease as does roentgen irradiation They may be of *great value in cases* where roentgen irradiation is no longer effective in those having severe systemic intoxication, or those with generalized lymphadenopathy, according to Jacobson *et al* (160) Nitro

[illegible] although nitrogen mustard appears to be a valuable adjunct to the therapy of Hodgkin's disease it does not replace roentgen ray *irradiation* In a com-

months with combined radiation therapy and 34 months for all cases, irrespective of therapy The five year survival rate was 24 per cent for patients treated with the Heublein method which was an improvement of 6 2 per cent over all cases of Hodgkin's disease treated at their clinic They concluded that "spray" irradiation, given alone, is not sufficient for lasting results, the greater the amount of previous therapy, the poorer the response Patients in the terminal stages of Hodgkin's disease did not respond to this therapy, the first treatments were the most beneficial and cases in which the local disease process was first controlled by local therapy showed the maximum improvement They found that this method of therapy may produce certain reactions, particularly gastrointestinal disturbance, weakness, apathy, fever, purpura or unfavorable blood changes This therapy should be administered with great caution to patients who have recently received large doses of irradiation and have leukopenia They also believed the Heublein method of treatment to be extremely impractical in most clinics since one x-ray machine must be used exclusively for treatment of only two patients for 20 or more hours

C Chemotherapy

1. Nitrogen Mustard. The most stimulating and promising current work in the chemotherapy of Hodgkin's disease is the use of B chloroethyl amines and sulfides, according to Hoster and Dratman (154c) They stated that 'these sulfur and nitrogen mustards are not only vesicants but also exert cytotoxic effects on a variety of tissues The susceptibility of cells to their action appears to be related to the rate of cell proliferation Mitotic arrest during the resting phase of the cycle is seen even after doses well below the toxic level, and extensive nuclear fragmentation is a consequence of somewhat higher doses Infectivity of the tobacco mosaic and bushy stunt viruses is lost after exposure to the mustard compounds These effects probably depend on reactions with important biological constituents of the cell The ability of the mustard compounds to interfere with enzyme systems in general has led to the enzyme inactiva

tion theory of their action in cells It has also been shown that solutions of casein exposed to mustard gas becomes in effective in supporting growth though they are not harmful when fed to animals Apparently the mustard compounds cause intramolecular changes in proteins and their residues, attached to amino acids like histidine lysine and methionine are not capable of being split off in the body The mustard compounds are especially useful when the disease is so widespread that it is impossible to treat it effectively with roentgen therapy Certain cases of Hodgkin s disease show negligible response to the drug most of these patients are said to be radio-resistant as well Large masses invasive lesions and foci in the skin and bone are said to be refractory to the [illegible]

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Zanes *et al* (360) stated that although nitrogen mustard appears to be a valuable adjunct to the therapy of Hodgkin s disease it does not replace roentgen ray irradiation In a com

parison of previously recorded results following roentgen ray therapy with those following the selective use of both roentgen radiation and nitrogen mustard therapy, they found that the combination of these therapeutic agents appears to offer greater hope for increased life expectancy than either modality, used alone

Dameshek *et al* (77) reviewed 50 consecutive cases of Hodgkin's disease treated with nitrogen mustard They found this therapy to be preferable to roentgen irradiation because of its rapid action, with the simultaneous reduction of all involved lymphoid tissue its greater effectiveness, particularly for the relief of pain pruritus and fever, and during remissions which had failed to respond to intensive roentgen ray therapy They believed, however, that roentgen irradiation is preferable in relatively early stages of the disease since the remissions are longer than with nitrogen mustard therapy For patients having jaundice or hepatic dysfunction, nitrogen mustard therapy is contraindicated The best results, they believed, may be obtained by the judicious combination of nitrogen mustard and roentgen ray therapy

The results of 151 courses of nitrogen mustard therapy, administered to 67 patients with Hodgkin's disease, were reported by Bierman *et al* (29) This series included 77 single injections of 0 2 to 0 4 mg per kg of body weight, and 35 single injections of 0 6 mg per kg The 13 patients who were in good or fair general health had remissions in about three months and responded better to nitrogen mustard therapy than the 11 patients who were in a poor or moribund state and had only a six week's remission One patient in the latter group showed no response to nitrogen mustard therapy Six patients developed severe toxic reactions following treatment which they believed, may have influenced the early death of four patients who developed pancytopenia and a hemorrhagic diathesis The large single dosage of nitrogen mustard employed in this series proved to be equally as effective as the usual four to six day course, which is usually administered

R Goldman *et al* (125) reported a series of cases in which

40 men having lymphomatous diseases were treated with nitrogen mustard. They found this therapy to be effective for Hodgkin's disease since the response to treatment is more prompt than with roentgen ray irradiation. However they found the remission period to be "of much shorter duration" although no serious toxic reactions were encountered in these cases.

In the series of cases reported by Zanes *et al* (360) 28 ✓ patients received "adequate" nitrogen mustard therapy. Among these 23 (82 per cent) patients benefited either through an immediate remission or by the apparent reestablishment of sensitivity to roentgen ray irradiation. The remaining five patients did not respond to this therapy and subsequently died. The patients who responded to nitrogen mustard therapy often had relief of pruritus, pain and occasional anorexia following the third or fourth injection. Fever was the most constant clinical finding during periods of exacerbation but the temperature returned to normal during therapy or within a week after completion of therapy. In one patient who had marked diffuse brownish cutaneous pigmentation the normal skin color returned two weeks after completion of therapy. A decrease in abnormal cutaneous pigmentation was also noted in two other patients. They found the toxic reactions to nitrogen mustard to be fairly consistent. The most serious complications following therapy resulted from bone marrow and lymphoid tissue destruction. The immediate toxic reactions noted were anorexia, nausea and vomiting which occurred within one half to three hours following treatment and developed in 38 of 44 courses administered. One patient developed diarrhea following therapy. Following the administration of 23 courses of nitrogen mustard 12 patients developed maculopapular markedly pruritic cutaneous lesions on the trunk and extremities within one to six weeks following treatment. This eruption began as markedly pruritic two to five mm sized pink maculopapular lesions which in some cases became hemorrhagic. The eruption was generalized in some cases while in others it was confined to one or more

extremities, or to a single area on the trunk, and usually persisted for a number of weeks They resembled the cutaneous lesions of Hodgkin's disease macroscopically but histologic examination revealed "vesiculobullous lesions presumably resulting from vascular damage The walls of the surrounding vessels showed marked degeneration" In addition to these maculopapular lesions, five patients developed classic herpes zoster One patient (case 14) was a 16 year old girl who had *severe generalized pruritus for six months, dark brown cu*taneous pigmentation and a generalized papular eruption with excoriations The pruritus and papular eruption disappeared 24 days after nitrogen mustard therapy was begun and the skin color became nearly normal

The causal factor in the development of cutaneous lesions following therapy in a number of these patients was not determined Zanes *et al* (360) could not ascertain whether this was due to the cutaneous spread of Hodgkin's disease following therapy, or to a toxic effect resulting from local or systemic vascular damage The profound leukopenia and thrombocytopenia observed following nitrogen mustard therapy reflects the extensive toxic damage to the hematopoietic system They found that the lymphocyte was the most rapidly destroyed of any of the formed elements of the peripheral blood The destruction of blood cell elements results from a central toxic effect as well as a peripheral one This is demonstrated by the concomitant destructive hypoplasia and aplasia of the bone marrow which is observed during the period when the peripheral blood count is lowest The bone marrow hyperplasia and the increased number of young forms of myeloid and erythroid elements, as well as the presence of megakaryocytes, while the peripheral cellular elements are increasing during the recovery stage, they believed would indicate the duration and temporary nature of this toxic effect on the blood cell forming precursors of the hematopoietic system

Podesta *et al* (259) reported almost complete healing of specific cutaneous lesions following nitrogen mustard therapy Their patient was a 20 year old man who had a painless, "wal-

nut" sized nodule in the right supraclavicular region of nine months duration Tumors appeared in the axillary and cervical regions and he developed profuse night sweats Seven months after onset of the disease pain in the sternal region severe dyspnea and cough developed and 7 200 cc of fluid was removed by repeated thoracentesis during a 25 day period Concurrently cutaneous nodules and tumors appeared in the thorax which were largely confluent on the right side The lesions which varied from the size of a grain of rice to a cherry were pale pink to deep red in color and many were ulcerated Histologic examination of a cutaneous lesion disclosed Sternberg Reed cells Treatment consisted of intravenous injection of 10 mg nitrogen mustard every second day for a total dose of 100 mg The cutaneous and lymph node lesions began to regress after half the total dose had been administered and the dyspnea diminished His general condition improved steadily during the month following treatment and the cutaneous lesions were almost completely healed Podesta *et al* believed the prognosis for patients having specific cutaneous lesions of Hodgkin s disease may become more favorable with the use of nitrogen mustard therapy

Thirteen patients in C A Hall and Olson s (136) series were initially treated with nitrogen mustard Six were given only nitrogen mustard and seven who were first given nitrogen mustard subsequently received roentgenotherapy later in the course of the disease Of these 13 patients 10 survived for the first year five the second three the third and one the fifth year following therapy Two patients did not have remissions while two had remissions of four and six years respectively Among 17 patients who were given nitrogen mustard following roentgenotherapy the results were "for the most part successful" In several cases the nitrogen mustard contributed to prolongation of the remission although in general the response was not as good as with previous roentgenotherapy None of their five patients known to be radioresistant showed significant response to nitrogen mustard therapy Among 10 patients who had previously received roentgenotherapy but whose re

sponsiveness had not been evaluated seven had "some response to nitrogen mustard therapy" All four patients who were known to be responsive to roentgenotherapy also responded to nitrogen mustard therapy. Craver (73g) stated that they administered the entire dose of 0.4 mg nitrogen mustard (Mustargen®) per kg of body weight in a single injection This single dose is given to patients whose blood platelet count and peripheral blood count are reasonably normal so that the reactions of nausea and vomiting, which usually follow the injection occur only one time.

2. ***Triethylene Melamine (TEM).*** Therapeutic results similar to those produced by the intravenous injection of nitrogen mustard have been induced in Hodgkin's disease, leukemias and some carcinomas by the oral administration of triethylene melamine (TEM), according to Karnofsky *et al* (168) and Rottino (282b) The advantages of triethylene melamine over nitrogen mustard therapy appear to be the oral administration (may be administered to ambulant patients), the infrequency of nausea and vomiting, which are preventable, and less difficulty in control of prolonged dosage However, nitrogen mustard is preferable when rapid control is desired because the effect of triethylene melamine may be slower It is necessary to carefully control the oral administration of triethylene melamine since the toxic reactions are the same as those of nitrogen mustard

The administration of oral therapy was discussed by Karnofsky *et al* (168) Triethylene melamine is available in 5 mg scored tablets which are taken with one half glass of water on awakening in the morning No food should be ingested during the following hour Nausea and vomiting may occur six or more hours later and continue for one or two days Regulation of the dosage to the amount which can be tolerated, from 2.5 to 5 mg will eliminate this reaction The initial course is 5 to 10 mg, of triethylene melamine If no change has occurred in the leukocyte count one week after treatment, another course of 5 to 10 mg is given Weekly observation of the patient is advocated, and further administration of this therapy is de-

pendent upon the leukocyte count the hemoglobin value and the general clinical condition of the patient If no improvement has occurred within three to four weeks and moderate leukopenia and anemia have developed it appears unlikely that any benefit will result from this therapy

The oral administration of triethylene melamine is most effective in the treatment of far advanced or generalized Hodgkin's disease according to Sulzberger *et al* (317a) Treatment usually causes reduction of fever pruritus weakness and anorexia and regressions in enlarged lymph nodes and tumors They treated 25 cases of Hodgkin's disease with oral triethylene melamine Among these patients 20 received some benefit from the initial course of treatment and of the 14 who had pruritus all had relief from treatment One of these patients a 45 year old man first developed cervical lymphadenopathy five years previously Axillary mediastinal and retroperitoneal lymphadenopathy occurred during the next two years but regressed following roentgenotherapy although the severe pruritus regressed only temporarily with this treatment Five years after onset of the disease the pruritus was resistant to roentgen irradiation and triethylene melamine was administered in doses of 35 mg over a five week period The pruritus promptly decreased in severity but recurred one month later There was again prompt relief with administration of 15 mg of triethylene melamine

3 *Colchicine* The advantages of colchicine therapy for Hodgkin's disease are reported to be the ease of administration the slight danger of reaction and the resultant symptomatic relief In describing this therapy Isch Wall (158) stated that the almost specific action of colchicine as a mitotic poison has previously gone virtually unnoticed because it is usually administered concurrently with roentgen ray irradiation as a means of increasing sensitivity to radiation and the favorable results were ascribed to radiation therapy He believed that apparently 20 to 30 injections should be given in a series He described four patients who were given only colchicine therapy The first intravenous injections of colchicine in doses of 3 mg

sponsiveness had not been evaluated seven had "some response to nitrogen mustard therapy" All four patients who were known to be responsive to roentgenotherapy also responded to nitrogen mustard therapy Craver (73g) stated that they administered the entire dose of 0 4 mg nitrogen mustard (Mustargen®) per kg of body weight in a single injection This single dose is given to patients whose blood platelet count and peripheral blood count are reasonably normal so that the reactions of nausea and vomiting, which usually follow the injection occur only one time

2. *Triethylene Melamine (TEM)* Therapeutic results similar to those produced by the intravenous injection of nitrogen mustard have been induced in Hodgkin's disease, leukemias and some carcinomas by the oral administration of triethylene melamine (TEM), according to Karnofsky *et al* (168) and Rottino (282b) The advantages of triethylene melamine over nitrogen mustard therapy appear to be the oral administration (may be administered to ambulant patients), the infrequency of nausea and vomiting which are preventable and less difficulty in control of prolonged dosage However, nitrogen mustard is preferable when rapid control is desired because the effect of triethylene melamine may be slower It is necessary to carefully control the oral administration of triethylene melamine since the toxic reactions are the same as those of nitrogen mustard

The administration of oral therapy was discussed by Karnofsky *et al* (168) Triethylene melamine is available in 5 mg scored tablets which are taken with one-half glass of water on awakening in the morning No food should be ingested during the following hour Nausea and vomiting may occur six or more hours later and continue for one or two days Regulation of the dosage to the amount which can be tolerated, from 2 5 to 5 mg will eliminate this reaction The initial course is 5 to 10 mg, of triethylene melamine If no change has occurred in the leukocyte count one week after treatment, another course of 5 to 10 mg is given Weekly observation of the patient is advocated, and further administration of this therapy is de

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the survival rate is no longer with surgery than with roentgenotherapy alone Gall (115) reported a 45 per cent five year survival and Hellwig (145) a 15 per cent five year survival following surgery However these patients apparently had a localized form of the disease and the results cannot be compared with other groups which include all clinical stages of the disease according to C A Hall and Olson (136) In their series of cases three patients were treated with local excision alone In two of these patients the disease was localized in the cervical lymph nodes Following removal of all obvious diseased tissue one patient had been free of symptoms for 12 years and the other had a recurrence eight years after surgery and was then given roentgenotherapy The third patient died one month after surgical removal of a tumor of the spinal canal However these investigators did not attribute the long survival of two of these patients to the surgery but rather to the benign nature of their disease They stated that the surgery in these cases was no more extensive than that performed at biopsy in many cases who respond poorly even with additional therapy

Six patients who were treated surgically for localized forms of Hodgkin's disease were reported by Bernard (26) Two patients were alive and well after six and eight years respectively He discussed the possibility of recovery by removal of the initial focus of the disease However this is seldom possible

A patient who had surgical removal of the cervical lymph nodes was observed by O'Brien (246) There was a recurrence in the supraclavicular lymph nodes 19 years later These nodes were also successfully removed surgically and the histologic examination revealed Hodgkin's disease

E Miscellaneous Therapeutic Agents

1 *Malarial Therapy* Malarial therapy has been used for cutaneous lymphomas When administered alone the results were not favorable "but when followed by x ray the response is striking" according to G R Murray (237)

2 *Artificial Fever Therapy* The use of a heated cabinet

every three days, for a total of 10 injections, were administered After three weeks of treatment there was a rapid decline of fever, regression of the lymphadenopathy and the general health improved to such an extent that one previously bedridden patient was able to resume his occupation Two weeks after treatment histologic studies revealed hyaline fusion of all the granulomatous tissue elements, producing a formless mass without recognizable cells Subsequent removal of material for histologic examination revealed caseation tissue present in an inguinal lymph node He obtained similar results from colchicine therapy in three other cases The red and white blood cell counts of the peripheral blood were not usually altered by this treatment However, in two patients who had *recurrence of symptoms, one had a decrease of leukocytes* from 6,000 to 3 000 cells per cu mm without agranulocytosis Both of these latter patients improved upon resumption of colchicine therapy

4. Steroids The influence of adrenocortical hormones on *Hodgkin's disease is not considered to be beneficial The real* value of these steroids is probably for management of complications and sequellae of the disease Hemolytic anemia may be followed by striking clinical improvement following administration of corticotropin (ACTH) or cortisone Steroid hormones may also be of some value in the management of severe bone marrow depression incident to therapeutic measures

Sulzberger *et al* (317a) reported a favorable response to corticotropin (ACTH) therapy in one case The patient was a 66 year old man who had cutaneous Hodgkin's disease He improved following ACTH therapy, which was administered in conjunction with local therapy This improvement continued after ACTH was discontinued but he subsequently developed two tumor like lesions on the back Sulman (316) also discussed the use of steroid therapy for Hodgkin's disease

D Surgery

There are comparatively few reports of the surgical treatment of Hodgkin's disease and these reports appear to indicate that

Craver (73g) He stated "*It seems* all too obvious that despite all the therapeutic agents that have been added in the past 15 years we still need something far better than what we have today The radioactive isotopes nitrogen mustards triethylenemelamine and similar chemical agents and the various hormonal agents have significantly contributed only to palliation"

to induce a body temperature of 106°F was described by Hoster (154a). There was no favorable response in three patients with Hodgkin's disease who were given this therapy.

3. Testosterone and Amino Acids. A patient with Hodgkin's disease who had only temporary regression with roentgen ray and anatoxic therapy over a five year period was described by Broco and Slucewski (45). During an acute episode treatment with male hormones, histidine, glycine and tryptophane was administered. The symptoms disappeared, normal activity was resumed and the patient appeared well 15 months after treatment. They believed that Hodgkin's disease may be alleviated with testosterone and amino acid therapy since the testosterone apparently lowered the fever and hypercalcemia, but increased the serum magnesium.

4. Vaccine and Serum Therapy. The antireticular cytotoxic serum of Bogomoletz (ACS) has been used for the treatment of Hodgkin's disease. Logically this serum would be expected to affect the reticuloendothelial system since it is an anti human bone marrow and spleen antibody, developed experimentally in an animal according to Hoster and Dratman (154c). ACS has usually been administered to patients having far advanced Hodgkin's disease. Although the results have not been favorable there was evanescent improvement. Because there have been no prolonged beneficial effects, it is difficult to evaluate the results of this therapy.

5. Antibiotics. The most recent approach to therapy has been the use of antibiotics notably by French investigators. Bertrand-Fontaine *et al* (28) used actinomycin for the treatment of Hodgkin's disease but the results were not encouraging. In the United States Martin and Munier (215a) reported the first results in 12 cases of Hodgkin's disease treated with actinomycin C and Krost and Meyer (215b) treated three cases with actinomycin D. Both studies provided these antibiotics to be of no value in the treatment of Hodgkin's disease.

Summary

The most effective summary to the problem of general treatment of malignant lymphomatous diseases is that given by

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PART THREE

LYMPHOSARCOMA

I.

DEFINITION

LYMPHOSARCOMA is a malignant neoplastic disease involving the lymphoid tissue. It is capable of arising in any lymphoid aggregate and may occur primarily or secondarily in the skin. The course of the disease may be acute or chronic and the lesions are nearly always radiosensitive.

II.

HISTORY

THE FIRST recognition of lymphosarcoma as a disease entity, distinguished from "aleukemic" lymphomas (pseudoleukemia), was made by Kundrat (84) Giant follicular lymphadenopathy, also known as Brill-Symmers disease, was described by Brill *et al* (14) and by Symmers (132b, d) and is usually regarded to have some relationship to lymphosarcoma In this monograph, there is no distinction of lymphosarcoma into the small round cell type and the reticulum cell type The cutaneous manifestations are the same in both of these types

III.

ETIOLOGY

Age and Sex In their study Sugerbaker and Craver (130) found lymphosarcoma to occur less frequently than Hodgkin s disease the ratio being 3 4 The average age on admission to the hospital was approximately the same for men and women 45 to 45 3 years respectively This was about 10 years more than in Hodgkin s disease and somewhat lower than in the more common types of carcinoma which at their clinic was 53 9 years Lymphosarcoma appeared to be rare before the age of 20 years and after the age of 70 years Their youngest patient was four years of age and the oldest 88 years although one of them had observed a proven case in a woman of 107 years By far the largest number of cases were of the reticulum cell type Three were histologically diagnosed as "malignant lymphocytoma and nine presented the histologic picture of giant follicular lymphoma They listed the age incidence of lymphosarcoma according to decades as follows

Age in Years	*Per Cent*
0–10	3 5
10–20	6 0
20–30	11 0
30–40	15 0
40–50	15 0
50–60	27 0
60–70	16 0
70–80	4 0
80–90	1 0

Lymphosarcoma occurred more frequently in men than in women according to Sugerbaker and Craver, with a ratio of about 7 3 while this ratio was 1 4 1 in Hodgkin s disease

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IV.

PATHOGENESIS

With our present knowledge, it is not possible to give any clear cut statement regarding the biologic forces which incite either lymphoid tissue, or any other tissue, to malignant growth. Its appearance following administration of indole, as reported by Bungeler (16), estrogens, as reported by Gardner (58), and injection of 1,2,5,6 dibenzanthracene, as mentioned by Lewis (90), indicate that the mechanisms stimulating lymphatic tissue to pathologic new growths are similar to, if not identical with, those activating other tissues (130).

The frequency of chronic infections, particularly long standing inflammatory processes in the upper respiratory tract of patients whose first evidence of lymphosarcoma appeared as a cervical lymphadenopathy, is rather striking. Sugerbaker and Craver (130) found 32 per cent of the patients whose first symptom was cervical lymphadenopathy complained of some definite chronic infection of the upper respiratory tract. The role of tuberculosis was much less evident in lymphosarcoma than in Hodgkin's disease, they found, and believed it not inconceivable that prolonged stimulation of lymph nodes may eventuate in malignant cellular activity. Ewing (44a) stated that subacute bacterial infections, particularly of the skin and mucous membranes are one of the common excitants of lymphatic tumors in both man and lower animals. Pyogenic cocci, especially streptococci are most prominent in this relation, although many other microorganisms may be present in some cases. That subacute streptococcic infection is capable of producing lymphocytic and reticulum cell hyperplasia instead of polynuclear leukocytic exudate, has been established. Fungus diseases, as well as staphylococcic and other cutaneous

Cutler (30) observed 13 patients having lymphosarcoma, four of whom had cutaneous involvement which was the tenth most frequent symptom of the disease Among 22 patients having cutaneous tumors of leukemia and lymphoma, reported by Gates (59), ten had lymphosarcoma Six were men, four women, and the median age was 56 years The duration of the cutaneous tumors was less than one month in one, one month in five, between seven and 12 months in two, and more than 12 months in five cases, while the median duration was six months Five patients had visceral metastases

Keim (80b) believed the incidence of metastatic cutaneous lesions to be about five per cent of the reported cases but stated that involvement of the mucous membranes, especially tonsillar, was more frequent Among 122 patients having lymphosarcoma, Epstein and MacEachern (42) found 29 (23 7 per cent) had cutaneous involvement and, of these, 17 had specific metastatic cutaneous nodules Gall and Mallory (57b) reported cutaneous involvement in from 17 to 26 per cent of the various types of lymphosarcoma classified Hellwig (69a) reported 11 of 145 patients having cutaneous involvement

or two minutes following the stimulus Cutaneous areas free of metastasis did not show the "white streak" Minute metastases, otherwise not demonstrable, could be discovered by this means He ascribed this reaction to the setting free, within the tumor nodules, of a base-like substance, and believed this picture did not correspond to that produced by histamine

According to Ewing (44b), lymphosarcoma is distinguished from other forms of lymphoma by its local destructive capacity and by the formation of true metastases in different organs arising in a chain of lymph nodes The tumors rapidly become bulky, infiltrate the surrounding tissue, and tend to cause ulceration and necrosis of the skin and mucous membranes Histologically, lymphosarcoma is generally divided into two groups 1) reticulum cell sarcoma or large round cell lymphosarcoma arising from the reticulum, and 2) malignant lymphocytoma arising from the lymphocytes Ewing believed that the two variants retain their separate identity and arise under different clinical conditions, in the great majority of cases

Since the cause or causes, of these diseases is not known there is need for a classification based on cytologic structure of the lesions, according to Director and Kern (36) This fact was also stressed by Gall and Mallory (57b) Klemperer (83) and Hellwig (69a) Ewing (44b) stated "The complexities of the subject of lymphoid tumors depend chiefly upon the lack of knowledge of etiology and partly upon lack of anatomical classification"

Roulet (119) described a group of tumors arising from lymphatic tissue as "retothelsarkom," which he believed were derived from reticulum cells of lymphatic tissue rather than from lymphatic cells In the classification of Ewing (44b), reticulum cell sarcoma is synonymous with large cell lymphosarcoma Such a classification is used by Ormsby and Montgomery (107c) Sugarbaker and Craver (130), and by Eller (41) The term "lymphosarcoma was introduced by Kundrat (84) who described it as a tumor arising not from a single lymph node but from a group of lymph nodes or from lymphoid tissue of a mucous membrane which after remaining localized

infections have been noted to precede lymphomatosis Local infection with regional lymphadenopathy has frequently occurred some months or years previously and, although the lymphadenopathy subsided, it recurred in the form of lymphosarcoma after a variable period of time In cases of deep lymphosarcoma, there may be a history of typhoid fever, appendicitis, cholecystitis, salpingitis or other local infection

The lymph node is the first barrier against infection which has passed the skin or mucous membrane, according to Ewing (44a) Free connections are present within the lymphatic system and with the blood vessels This relationship may account for the tendency of lymphatic diseases to become systemic He believed the possibility exists that growth stimulating cell products, diffusing from the primary tumor focus, may play a part in the remarkably wide and rapid extension of some lymphatic tumors At times the entire lymphatic system seems to react as a whole

Berghausen (7) observed two patients having both lymphosarcoma and syphilis, a combination of diseases he believed to be infrequent The first patient had marked generalized lymphadenopathy but severe splenomegaly and enlargement of the abdominal lymph nodes pointed to the clinical diagnosis of lymphosarcoma The second patient had marked peripheral lymphadenopathy chiefly cervical at the onset, and Hodgkin's disease was considered Both patients had specific syphilitic infection and the blood serologic reaction (Wassermann) was strongly positive Post mortem examinations were done on both patients Combes (26b) stated that Trimble's case of "erythema elevatum diutinum" eventuated in a fatal lymphosarcoma

Auler (2) described an allergic phenomenon associated with cutaneous metastases of generalized lymphosarcoma He found evidence of allergy by stroking the skin with a needle point in an area involved by metastasis of lymphosarcoma In the line of the stroke, a white streak (white dermographism) promptly appeared This streak gradually widened and about the metastasis a red zone resembling urticaria appeared one

blasts" by Ferrata (48), and as "common lymphoid stem cells" by Gall and Mallory (57b) They have probably been most frequently designated "reticulum cells," as by Klemperer (83), Ewing (44b), Roulet (119), Sugerbaker and Craver (130), Edling (38), Callender (18), and Herbut *et al* (70) The nature of the primitive reticulum cell was summarized by Ehrlich and Gerber (39) who stated that 'there has been accumulated a convincing array of evidence to substantiate the view that the cytoplasmic reticulum present throughout the body, in the spleen, lymph nodes, liver, bone marrow, and perivascular tissue, retains in adult life the multipotency of embryonal mesenchyme"

Various investigators have observed the steps in the transformation of the reticulum cell into the lymphocyte in the embryo, in tissue cultures and in the adult, according to Klemperer (83) The concept of a widely distributed multipotent primitive mesenchymal cell (reticulum cell) which, as a result of certain stimuli, acts as a lymphoid stem cell, best explains the nature and histologic structure of these conditions, generally included among the lymphomas, he believed The classification proposed by Gall and Mallory (57b) is based upon the predominant cell of the tumor, each cell type being recognized as representing a stage in the development of the lymphocyte from the reticulum cell They divided malignant lymphomas into the seven following groups 1) stem cell lymphoma, 2) plasmatocytic lymphoma, 3) lymphoblastic lymphoma, 4) lymphocytic lymphoma, 5) Hodgkin's lymphoma 6) Hodgkin s sarcoma, and 7) follicular lymphoma

Stem cell lymphoma corresponds to the reticular and intermediate types of lymphosarcoma described in detail by Ehrlich and Gerber (39) The reticular type consists primarily of nuclei dispersed in a cytoplasmic syncitium without clear boundaries The nuclei are very large, 10 to 12 microns in diameter are oval usually vesicular, with a moderately thick, darkly staining nuclear membrane, frequently infolded Mitotic figures are often observed and are usually of normal configuration One to three nucleoli are present In the inter-

for an indefinite period, spread either by direct extension or through the lymphatics However, many investigators, including Gibbons (60), Flashman and Leopold (51), Baldridge and Awe (4) and Brunschwig and Kandel (15), have objected to the term "lymphosarcoma" Gall and Mallory (57b) stated that "such a segregation is artificial and merely represents a phase in the course of the disease"

Knowledge concerning the reticulum cell was first obtained through the discovery of a network of stellate cells forming the framework of the splenic pulp by Tigri (134) in 1847 Shortly thereafter, this reticulum of cells and fibrils was found to exist in lymphatic, as well as in splenic tissue The similarity between the reticulum cells of the embryonal spleen and those of the adult spleen was pointed by Klemperer (83) Not only is this similarity morphological, but the cells also possess the same developmental potentialities Each is capable of differentiation along four lines, with the formation of hematic phagocytic, endothelial and fibroblastic cells The reticulum of lymphoid and myeloid tissue can according to Maximow (97), be considered "an embryonal germinal layer of the adult organism"

Foot (52) stated that more difference of opinion exists concerning the diagnosis of reticulum cell sarcoma than that of almost any other type of lymphoid neoplasm He believed this may be due to the fact that there are two distinct branches of the reticulum family, that resident in the lymph follicles and that found in the areolar connective tissue Some pathologists will not admit that a reticulum cell sarcoma can arise in the latter situation calling such tumors fibrosarcomas" However, as a result of animal experimentation and tissue culture, Maximow (97) concluded that cells having the same developmental potentialities as the reticulum cells are scattered throughout the body In the skin these cells (which he called undifferentiated mesenchymal cells) are perivascular These primitive cells have been referred to as "lymphoidocytes" by Pappenheim (109), "primitive blood cells" by Farrar and Cameron (46), 'hemocytoblasts' by Turnbull (135), "histio

(36) indicates that this growth too is derived from the reticulum cell

There are numerous reports of transformation from one type of lymphoma to another Gall and Mallory (57b) found that 23 2 per cent of their cases of malignant lymphoma showed on repeated histologic examination a change in structure toward less differentiation Hellwig (69i) found that 20 per cent of his cases showed a change toward less differentiation with 80 per cent retaining the original histologic structure Herbut *et al* (70) described six cases which histologically showed various transformations between Hodgkin s disease reticulum cell sarcoma and what they described as lymphosarcoma It is believed therefore that all malignant lymphomas are derived from one source the reticulum cell and that the development of a given form or the transformation from one type to another depends on unknown stimuli acting on this cell

Since the reticulum cell is not limited to the spleen and lymph nodes as was originally considered Robb Smith (117) commented "we do not need to explain generalized tissue changes as a result of embolization or metastases but may regard them as local proliferations of mesenchymal cells"

Director and Kern (36) stated that the present tendency is toward a belief that all diseases grouped as "lymphoblastomas even though not due to the same cause produce histopathological changes in which the essential diseased cells are the primitive mesenchymal reticulum cells and their developmental derivatives These primitive cells are widely spread throughout the body so that other tissues such as the skin may give rise to a primary focus of the disease and the condition need not arise primarily from lymph nodes or blood forming tissues

Szathmáry (133) divided lymphosarcoma of the skin into two types The localized regional primary manifestation or evidence of involvement of and extension along lymph channels He regarded lymphosarcoma of the skin secondary to a localized process in the deeper groups of lymph nodes as most infrequent The second type belongs to the Paltauf Kundrat

mediate type, the cellular constituents are partly in syncytial arrangement and partly discrete According to Gall and Mallory (57b), the fundamental similarity between these two types is so great that their separation into distinct entities is not justified Varying numbers of lymphocytes and monocytes are observed in these tumors, and the fibrillar reticulum is comparatively sparse The second constituent of the reticulum cell sarcoma group in this classification by Gall and Mallory (57b), the clasmatocytic lymphoma, has as its predominant cell the clasmatocyte or monocyte This cell is described as smaller than the stem cell but distinctly larger than the lymphocyte with pronounced phagocytic properties They believed that clasmatocytic lymphoma should be classified as a monocytoma Hellwig (69a) suggested removal of the clasmatocytic lymphoma from the reticulum cell sarcoma group in this classification, since the cells comprising this tumor are not actually primitive reticulum cells but rather have differentiated from them, and have taken on the function of pronounced phagocytosis

When clasmatocytic lymphoma is made a distinct entity, the stem cell remains as reticulum cell sarcoma, according to Director and Kern (36) Regarding the remaining five classifications, lymphoblastic lymphoma is characterized by the predominance of lymphoblasts In lymphocytic lymphoma, the lymphocyte is the predominant cell In follicular lymphoma, the lymphocyte is again the predominant cell but the tumor has a distinct architecture with the normal lymph node structure replaced by multiple, varying sized, follicle-like nodules If Hodgkin's disease is accepted to be a primary malignant tumor it may be considered to be derived from the reticulum cell, since the pathognomonic Sternberg-Reed cell is probably a reticulum cell which according to Gall and Mallory (57b), has become large and multilobulated or multinucleated Callender (18) and Richter (115) maintained that Hodgkin's sarcoma and reticulum cell sarcoma are identical Whether or not one accepts the existence of Hodgkin's disease *per se*, the evidence at hand, according to Director and Kern

symmetrical tumor formation in the salivary glands Primary lymphosarcoma occurring in a 19 year old child who developed typical lymphocytic leukemia following roentgenotherapy, was also described Berde and Lang (6) observed a patient having multiple small cutaneous nodules which they regarded as benign probably of endothelial origin They found lymphosarcoma recorded in only 21 specific instances in the literature prior to their report Among 30 cases of lymphosarcoma, Cutler (30) found cutaneous and subcutaneous involvement in only four of the 13 cases in which post mortem examination was done Primary cutaneous involvement was also described by Holmes and Schulz (71) Matheson (96) described primary lymphosarcoma of the neck in a 26 year old man who had extension into the abdomen mesenteric lymph nodes liver and subcutaneous tissue of the chest and abdomen

Squires (126) reported lymphosarcoma with extension into the skin proved histologically before lymphadenopathy occurred There were also pigmented cutaneous macules papules and nodules Menne and Bitar (99) believed the fact that this patient also had a three plus blood serologic (Kahn) reaction might be significant especially since the various cutaneous lesions described did not adhere to the usual appearance of cutaneous lymphosarcoma In a study of 445 patients having "lymphoblastomatous" diseases Epstein and MacEachern (42) found that specific cutaneous lesions occurred in 13 9 per cent of the cases and they believed these metastatic nodules to be the most frequent dermatologic finding McNamara and Henneger (95) described a patient who had gener l od the

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quite remote from the site of origin is difficult to explain according to Menne and Bitar (99) Gates (59) regarded cutaneous invasion as definitely metastatic Often the occurrence of a new crop of cutaneous nodules is contrary to the flow of lymph The best assumption according to Menne and

group in which the lesions are either definitely primary in the skin or in closely contiguous lymphatics He found reports of only three cases of the first type among them the case described by Joseph (77) He also described two cases of this latter type occurring in men aged 29 and 18 years respectively The latter patient developed "pea to hazel nut sized livid red cutaneous nodules of the epigastrium and right side of the tongue within a period of eight days The cutaneous involvement in both patients occurred secondary to primary mediastinal tumors Histologically the majority of cells were of lymphocytic type and there were some polymorphonuclears and lymphoblasts Subsequent reports however do not give definite evidence of a sharp division of the two distinct types of lymphosarcoma mentioned by Szathmary according to Menne and Bitar (99) They stated that most investigators have apparently divided lymphosarcoma of the skin into two groups those having evidence of localized cutaneous lesions with localized spread and those having regional involvement which gives rise to a general extension in the skin and not infrequently into other internal organs

Claus (24) reported the occurrence of a tumor of the ear in a girl two years and nine months of age Harrington *et al* (66) described a 35 year old woman who had lymphosarcoma occurring between the second and third ribs and extending into the cutaneous surface up over the chest wall Shebesta (125) described cutaneous lymphosarcoma of the face in a 33 year old man in whom the lesion was apparently primary in the maxillary antrum Menne and Bitar (99) believed that such lesions were not so much metastatic dissemination of cutaneous lymphosarcoma as extensions into the skin by continuity These types they stated are in sharp contrast to those having extensive infiltration of the cutaneous and subcutaneous tissues to the end that not infrequently the involvement of the skin may completely overshadow the primary site of origin Bettmann (9) reported a patient having disseminated lymphosarcoma of the skin with secondary nodules in the conjunctivae associated with slight lymphadenopathy and a

V.

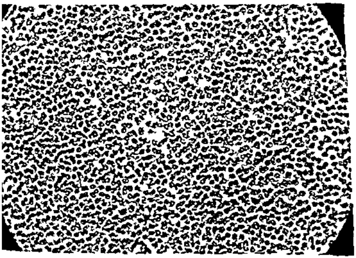
PATHOLOGY

THE MORBID anatomy of lymphosarcoma was reviewed by Sugerbaker and Craver (130) who stated that lymphoid tissue just as other tissue may assume malignant properties The sites of origin are potentially as widespread as the distribution of lymphoid aggregates throughout the body The unit of lymphoid tissue the lymph follicle being composed of two distinct and easily identifiable types of cells (the reticulum or endotheloid cells of the germinal center and the small lymphocytes arranged peripherally about these centers) may give rise to two corresponding histologic types of sarcoma the reticulum cell type or reticulum cell lymphosarcoma and the lymphocytic type or malignant lymphocytoma The exact physiologic tie between these two types is not definitely established although their anatomic juxtaposition bolstered by the clinical observation of the not infrequent termination of reticulum cell lymphosarcoma into lymphocytic leukemia strongly suggests the existence of a very definite though as yet obscure relationship It seems reasonable they believe to consider tumors composed of either cell type exhibiting malignant properties simply as variations of the same disease namely lymphosarcoma until contrary proof is found

Symmers (132c e) stated that the lymph nodes in lymphosarcoma present much the same microscopic appearance as those in Hodgkin s disease The individual lymph nodes vary in size from a few millimeters to many centimeters and may be arranged in groups or in chains They are usually closely packed and their shapes may be altered by pressure reciprocal or otherwise On dissection they are discrete the more acces

Bitar, appears to be that the cells spread by way of the blood circulation If so, it is not easy to explain the regional selective character of the metastases It has been suggested that universal irritational hyperplasia of cutaneous lymphatic cell groups may develop, either simultaneously or progressively, being stimulated by the same etiologic agent



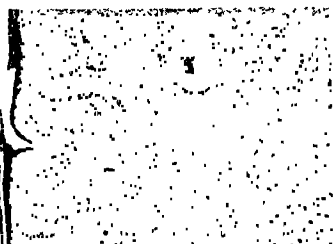


1 Lymphosarcomatous lymph node showing obliteration of normal lymph node structure

2 High power magnification of Figure 1 showing the reticulum cells of one of the nodules

sible nodes are apt to give this impression when palpated through the overlying structures and their consistency varies and is determined by the amount of connective tissue present Usually they are relatively soft because the stroma is seldom abundant and each is surrounded by a thin capsule and film like sheets of connective tissue between the nodes The substance of the node bulges somewhat beyond the cut edge of the capsule and varies in color from pure or greyish white to a faint brownish sheen but may be a pinkish hue if the delicate connective tissue reticulum and the normal node structure is well supplied with capillary blood vessels On microscopic examination the lymph nodes show overgrowth of lymphocytes in the connective tissue reticulum and the normal node structure is obliterated Frequently the capsule is infiltrated by the same type of lymphocytes which prevail in the parenchyma and the internodal connective tissues are often invaded according to Symmers

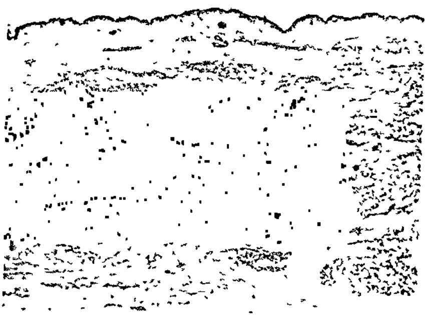
Brill *et al* (14) and Symmers (132d) described several cases of lymphadenopathy often accompanied by splenomegaly in which the lymph node picture showed "numerical and dimensional follicular hyperplasia (Symmers) The dimensional increase in the follicle apparently results from proliferation of cells within the germinal centers Whether or not such cases represent a separate clinicopathological entity is doubtful Later Symmers (132e) stated that in certain instances at least a transition to Hodgkins sarcoma or to a polymorphous cell sarcoma (lymphosarcoma) is apparent in late histologic studies or to lymphocytic leukemia as shown by successive blood counts may eventually occur in giant follicle lymphoma Sugerbaker and Craver (130) tended to regard giant follicular lymphomas as an early setting for lymphosarcoma usually destined to run a somewhat less acute but otherwise typical course and late histologic studies in several of their cases showed typical reticulum cell lymphosarcoma They believed it difficult to decide exactly where to place Hodgkins sarcoma Callender (18) would combine





5 Large mass of loosely packed lymphosarcoma cells involving the entire corium
6 Close-up of Figure 5 (Squared area)





3 Lymphosarcoma cutis showing the subepidermal portion of the cutis to be spared

4 Densely packed lymphosarcoma cells producing nodules in the cutis

it and reticulum cell sarcoma into a single group designated "reticulum cell sarcoma"

Histopathology of the Skin Although primary lymphosarcoma of the skin is a relatively infrequent manifestation it may occur as solitary or multiple cutaneous nodules or even as an exfoliative dermatitis

The epidermis is not involved and the subepidermal portion of the cutis is usually spared This is an important point in the histologic differentiation of lymphosarcoma and mycosis fungoides

The cutaneous nodules of lymphosarcoma usually consist of compact masses of cells in the mid and deep cutis The cells are usually of a uniform character and may show mitotic figures This feature is a further aid in differentiating lymphosarcoma from the leukemias The masses of tumor cells are well circumscribed and suggest secondary (metastatic?) involvement rather than autochthonous development in the skin The wall of a blood vessel deep in the cutis may be infiltrated with cells in some sections Usually the cells are immature

Occasionally the cells tend to invade the cutis in strands The bundles of collagen fibers are pushed aside by the cells which appear in large masses

The type of lymphosarcoma is dependent upon whether small lymphocytic cells or reticulum cells predominate although a combination of both types of cells may be present However the reticulum type cell is most frequently present They present an abundant pale staining cytoplasm and variously shaped nuclei Mitoses are usually present



7 Sheets of lymphosarcoma cells in the cutis
8 Reticulum cells showing pale-staining cytoplasm and variously shaped nuclei





9 Cervical lymphadenopathy
10 Cervical lymphadenopathy



11 Axillary lymphadenopathy

VI.

CLINICAL FEATURES

Lymphosarcoma, like Hodgkin's disease, appears to begin as a localized disease, according to Craver (29a). Its onset is usually in one of three regions the nasopharyngeal ring of lymphoid tissue, the mediastinal lymph nodes or thymus and in the abdomen, most likely from the gastrointestinal nodes or perhaps the lymphoid tissue of the alimentary canal The lymph nodes tend to be more diffuse than in Hodgkin's disease, which Craver believed may be due to the tendency of lymphosarcoma to infiltrate the fat tissue outside of the capsule of the nodes It is very striking that patients with lymphosarcoma tend to remain in much better condition than those with Hodgkin's disease

Visible and palpable lymphadenopathy was the initial symptom in 65 per cent of Sugarbaker and Craver's (130) patients The enlargement was entirely painless in nearly all cases although occasionally pain traceable to infiltration of the cervical plexus occurred when there was massive swelling of the neck Lymphosarcomatous nodes generally tend to have a characteristic resilient firmness Although the entire chain is usually involved, a solitary enlarged lymph node may occur They tend to be fixed Other initial symptoms, described by Sugarbaker and Craver were abdominal discomfort, which occurred in 17 5 per cent of their patients, upper respiratory symptoms in 11 6 per cent thoracic symptoms in 3 6 per cent and bone pain in 1 83 per cent They found systemic symptoms (chills, fever lassitude increased sweating, weight loss) to be conspicuously absent in early lymphosarcoma, rarely appearing until the disease was far advanced An extranodal focus of disease was found which could reasonably be

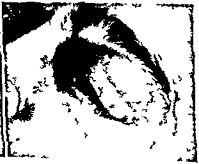
symptoms which are frequently alarming. This pressure on the superior vena cava and jugular vein causes the face to become swollen and congested with distended veins in the neck. Compression of the trachea makes breathing difficult and there is an inspiratory stridor and marked hoarseness. If pressure on the deeper veins in the thorax occurs, there may be pleural effusion or chylous effusion may result from pressure on the thoracic duct. Effusion is less common in lymphosarcoma than in Hodgkin's disease.

Mikulicz's Disease. Mikulicz's disease is a symptom complex characterized by symmetrical lymphadenopathy of the lacrimal, orbital and salivary glands due to infiltration of small round cells. The predominant clinical signs and symptoms are caused by pressure from the enlarged lymph nodes and dryness of the mouth and throat; exophthalmos and impaired hearing and vision may occur.

A relationship between Mikulicz's disease and lymphosarcoma was first suspected in 1889 when Adler (1) reported this association. Although there is usually involvement of all the salivary and both lacrimal glands, Kerschbaumer (82) described a patient having involvement of only the lacrimal glands.

This syndrome associated with lymphosarcoma has been





12. Lymphosarcoma of the lacrimal gland.
13. Lymphosarcoma of the lacrimal gland. (*A.M.A. Arch. Dermat.* Bluefarb (Feb.) 1956)

assumed to represent the primary site in only one third of the patients examined

Site of Focus	*Per Cent*		*Site of Focus*	*Per Cent*
Tonsils	14		Bone	1
Nasopharynx	5		Prostate	1
Parotid	1	Head 22 per cent	Testicle	1.5
Antrum	1		Ovary	0.5
Orbit	0.5		Breast	0.5
Eyelid	0.5		Lung	0.5
			Thymus	1
			Skin of Arm	0.5
Stomach	3			
Jejunum	1	Gastrointestinal 5.5 per cent		
Ileum	1			
Rectum	0.5			

Total cases presenting an extranodal primary focus 34.5 per cent

Craver (29b) stated that lymphosarcoma of the tonsil is frequently overlooked for a long period and "any peculiar irregularity or firm rubbery part of a tonsil should be regarded with suspicion." Lymphosarcoma of the tonsil seldom ulcerates in an early stage. He believed that "all tonsils that are removed, especially from patients beyond the age of puberty," should be examined histologically.

Sugerbaker and Craver (130) believed it logical to assume that lymphosarcoma is a disease which in the majority of cases, begins and runs its early course in the lymph nodes alone. They believed that lymphosarcoma is generally an acutely malignant disease and although chronic forms do occur, they are a small minority. Metastasis is apt to be sudden and widespread and may involve any organ or tissue. Lymph node involvement eventually occurs in all cases unless death occurs from gastric hemorrhage, intestinal obstruction, or some unrelated cause. At first the disease is largely confined to the lymphatic system, contiguous node groups may become involved in rapid sequence or even simultaneously. They described the presenting symptoms as generally thoracic presssure

symptoms which are frequently alarming This pressure on the superior vena cava and jugular vein causes the face to become swollen and congested with distended veins in the neck Compression of the trachea makes breathing difficult and there is an inspiratory stridor and marked hoarseness If pressure on the deeper veins in the thorax occurs there may be pleural effusion or chylous effusion may result from pressure on the thoracic duct Effusion is less common in lymphosarcoma than in Hodgkin s disease

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12 Lymphosarcoma of the lacrimal gland
13 Lymphosarcoma of the lacrimal gland (A M A *Arch Dermat* Bluefarb (Feb) 1956)

emphasized by Fernandez et al (49) Hardesty (65) and Schaffer and Jacobsen (121) A 43 year old woman reported by the latter died three years after the Mikulicz's disease appeared Symmers (132a) patient had symmetrical conjunctival lymphosarcoma a manifestation he believed to be related to Mikulicz's disease

Leucutia and Price (88) reported a 57 year old woman who had a rather generalized small round cell symmetrical extension of the process to the lacrimal glands All the tumors melted away following radiotherapy Cornbleet and Pace (28a) presented a seven year old Negro boy who had bilateral parotid lymphosarcoma The salivary and lacrimal lymph glands later became involved A 25 year old woman reported by Isaurraulde and Imaz (74) had enlargement of the lacrimal parotid submaxillary and sublingual lymph glands of two months duration She also had generalized lymphadenopathy and numerous cutaneous nodules which proved to be lymphosarcoma on histologic examination

Other cases of this association have been described by Axenfeld (3) Caspary (20) J R Miller and Eusterman (101) Pooley (113) Wallenfang (138) and Ziegler (146) These cases represent secondary localizations of the lymphosarcomatous process

Case Report A 79 year old Negro first developed a slowly progressive swelling of the neck associated with weakness and malaise one year previously On examination he was emaciated chronically ill and markedly deaf There were large "stony hard matted cervical lymph nodes which extended up both temporal regions resulting in a frog like" appearance of the face He had generalized lymphadenopathy which was most marked in the cervical regions

Since a diagnosis of chronic lymphocytic leukemia had been considered on a previous examination the peripheral blood and bone marrow studies were reviewed A diagnosis of small round cell lymphosarcoma was then established The peripheral blood revealed 71 per cent hemoglobin 4 130 000 red blood cells and 4 100 white blood cells per cu mm with 46

per cent polymorphonuclears, 28 per cent lymphocytes 2 per cent eosinophils 11 per cent monocytes 3 per cent metamyelocytes and 10 per cent band forms

He was given roentgenotherapy to the large nodules in the neck and to relieve the mediastinal obstruction

Two other examples of Mikulicz's disease are illustrated





14 Mikulicz's disease (case report) (A M A *Arch Dermat* Bluefarb (Feb) 1956)
15 Mikulicz's disease

Internal Organ Involvement In addition to the primary sites of involvement intranodal or extranodal numerous organs may subsequently become involved either as a result of lymphatic or hematogenous metastasis or by direct extension The organs involved later in the course of the disease presumably as a result of hematogenous or lymphogenous spread are listed by Sugarbaker and Craver (*130*) as follows

Organ	*Per Cent*	*Organ*	*Per Cent*	*Organ*	*Per Cent*
Spleen	21	Stomach	2	Brain	0 5
Lungs	12	Testes	1 5	Larynx	0 5
Bones	9	Spinal cord	1 5	Lacrimal gland	0 5
Liver	8	Breast	1	Orbit	0 5
Skin	5 5	Bladder	1	Conjunctiva	0 5
Intestinal tract	5	Penis	0 5	Tongue	0 5
Tonsils	3	Ethmoids	0 5	Palate	0 5

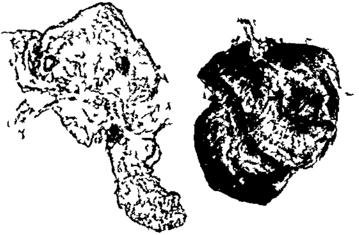


16 Mikulicz's syndrome

Among 31 cases of lymphosarcoma Videbæk (137) listed the following symptoms

Initial Symptoms	No. Cases	*Later Symptoms*	No. Cases
Lymphadenopathy	18	Lymphadenopathy	21
Dysphagia	6	Fatigue and weight loss	9
Fatigue	4	Splenomegaly	8
Cough and expectoration	1	Hepatosplenomegaly	4
Cutaneous infiltrates	1	Sore throat	7
Nasal obstruction	1	Cutaneous infiltrates	4
		Fever	6
		Pain	2
		Pruritus	1

"Metastatic" cutaneous involvement is reported to occur in about 5.5 per cent of the cases. Intracutaneous nodules are usually quite firm but lack the hard consistency of carcinomatous nodules and usually have a shiny bluish red appearance according to Sugerbaker and Craver (130). When there is evidence of hematogenous spread (as in lungs, bone, skin and spleen) the prognosis is extremely grave and the life expectancy



17. Lymphosarcoma of the stomach and liver

is usually very short. They believed the rapidity with which lymphosarcoma advances is readily understood when one considers that the average duration of life from onset to death is 20.5 months.

The hemogram is not specific in lymphosarcoma. Sugerbaker and Craver (130) found that in contradistinction to patients having Hodgkin's disease, in whom anemia usually develops early in the disease (32 per cent on admission), lymphosarcoma patients maintain excellent hemoglobin values for some time. On admission 70 per cent of their patients showed hemoglobin values above 80 per cent and only 10 per cent of the patients

had less than 70 per cent hemoglobin The total white blood cell count on admission was above 7,500 in 53 per cent of the cases, 23 showed leukocytosis with a count above 10,000, and 18 per cent had less than 5,000 white blood cells per cu mm of blood Cells of the granulocytic series predominated

Craver (29b) stated that "It cannot be too strongly emphasized that any enlarged lymph node demands immediate investigation Entirely too frequent is the story of an enlarged lymph node in the neck being passed off as the result of a cold or sore throat Any supposedly inflammatory enlarged node that does not subside within three weeks should be regarded as a danger signal demanding complete investigation Such investigation should include competent examination of the drainage territory of the node (for example, search of the nasopharynx, tonsil and adjacent areas for a possible primary lymphosarcoma in the case of an enlarged node in the upper cervical region), biopsy of the primary lesion if one is found biopsy of the node if no primary lesion is found, a careful blood cell count, and of course, a complete physical examination for enlargements of other lymph nodes or of the spleen or liver If, as often happens in early Hodgkin's disease or lymphosar cold or sore throat Any supposedly inflammatory enlarged node, which is reported after biopsy as chronic lymphadenitis or at any rate failing to show evidence of any definite pathologic entity, and if then other nodes appear near the site of the originally enlarged one, there should not be undue delay before biopsy is made of another node which seems on palpation to be representative of something abnormal

"Cough, substernal pressure fullness at the base of the neck and puffiness of the eyes on arising wheezing, and dyspnea are symptoms any or all of which should indicate the need for a competent straight postero anterior and straight lateral roentgenogram of the chest and, if necessary, oblique roentgenograms and tomograms to exclude a mediastinal tumor, which might be Hodgkin's disease or lymphosarcoma, among other possibilities In such cases significant lymph nodes lying at the base of the neck especially between the two lower inser-

tions of the sternocleidomastoid muscle, are often overlooked because of failure of careful palpation with a light pressure A gentle palpation with moistened fingers may disclose a node that was missed on rough palpation'

had less than 70 per cent hemoglobin The total white blood cell count on admission was above 7,500 in 53 per cent of the cases, 23 showed leukocytosis with a count above 10,000, and 18 per cent had less than 5,000 white blood cells per cu mm of blood Cells of the granulocytic series predominated

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dent with the resumption of roentgenotherapy to the chest wall all pruritus disappeared

McGlasson and Lehmann (94) described a 25 year old woman who complained of generalized pruritus She presented scratch marks and other evidence of traumatism to the skin which otherwise appeared normal Cole (25) reported an 18 year old boy who had lymphosarcoma associated with pruritus which was a troublesome symptom of the disease That pruritus is a manifestation of disease of the lymphatic nodes was well illustrated by Blaschko's (12) case This patient a young man with lymphosarcoma of the cervical lymph nodes manifested an intolerable pruritus which disappeared two days after excision of the involved nodes but recurred with the reappearance of lymphadenopathy

A 33 year old woman who had reticulum cell lymphosarcoma associated with cryoglobulinemia was described by Pascher (110) She had "cold urticaria for three successive winters which was followed by purpura and aggravated by exposure to cold This was elicited by the application of ice packs to the skin which was followed by a purpuric eruption most marked on the lower extremities resembling the so called "pigmented lichenoid eruptions of the lower extremities" Cryoglobulins were demonstrated in the blood Hypertension albuminuria progressive hepatosplenomegaly and retinitis appeared before death Autopsy revealed reticulum cell lymphosarcoma of the lungs liver spleen and lymph nodes and periarteritis nodosa of the heart aorta and abdominal viscera

Prurigo-like Papules Prurigo like papules (prurigo lymphadenique) occur with lymphosarcoma just as in leukemia and Hodgkin's disease and have been described by Dubreuilh (37) and Wunderlich (144)

MacVicar (91) presented a 57 year old Negro who had a prurigo like cutaneous eruption associated with lymphosarcoma His initial symptoms were pruritus and cervical and inguinal lymphadenopathy Histologic examination of a lymph node revealed lymphosarcoma Transient papules and nodules

VII.

CUTANEOUS LESIONS

A. Nonspecific Lesions

Desjardins and Ford (34) found that the nonspecific cutaneous manifestations of Hodgkin's disease and lymphosarcoma show a close parallelism.

Pruritus. Pruritus occurred somewhat more frequently in Hodgkin's disease (9 per cent of 135 cases) than in lymphosarcoma (3 per cent in 102 cases) according to Desjardins and Ford (34).

Wise (142) described a 39 year old man who complained of severe generalized pruritus, dryness and a creeping sensation of the skin. The pruritus which began on the calves of the legs gradually became generalized. He presented many noninflammatory scratched papules over the extremities, shoulders and back, and dime to palm sized brownish slightly scaly macules on the hips and trunk. The legs were slightly edematous. There was splenomegaly and a hazelnut sized right inguinal lymph node which revealed lymphosarcoma on histologic study. Wilhelm and Goeckerman (141) described generalized lymphosarcoma in a patient who had an intense deep seated pruritus.

Cornbleet *et al.* (28b) reported reticulum cell sarcoma associated with generalized pruritus in a 72 year old man who had a mass above the right scapula which had been present for nine months. This mass grew to the size of a small grapefruit within a few weeks and simultaneously small cutaneous tumors appeared on the chest and neck. Roentgenotherapy caused reduction in size of the large tumor and disappearance of the others. There was some relief from the generalized pruritus with large doses of salicylates but concur-

was ineffective and she died two months later from generalized lymphosarcomatosis

A 72 year old man described by Keim (80a case 4), presented an ulceration of the junction of the hard and soft palates and a generalized cutaneous eruption on the trunk and extremities There were vesicular lesions scattered in many groups varying from "pea to orange" size and *many vesicles* had ruptured the serum drying in a yellowish adherent crust The lesions were superficial markedly inflammatory and on involution left areas of brownish hyperpigmentation The condition was believed to be dermatitis herpetiformis

A patient having a granulating cutaneous ulcer of the left forearm and a nonspecific papular eruption in the deltoid region and gluteal folds was reported by Ingels (73) The eruption resembled that of secondary syphilis An ulcer on the forearm proved to be lymphosarcoma on histologic examination

A patient having prurigo like papules of the face associated with lymphosarcoma occurring behind the right eyeball causing a proptosis is illustrated

Case Report A 23 year old man first developed progressive nasal obstruction bilateral deafness and cervical lymphadenopathy four months before admission to the hospital Generalized lymphadenopathy had then been present for several weeks and he had a large mass of tissue in both lateral pharyngeal walls *There were numerous large soft nontender lymph* nodes in the cervical post auricular submaxillary and right occipital regions The histologic examination revealed lympho sarcoma One month later he complained of persistent sore th o t h

s o cu sor e

residual pigmentation The cutaneous eruption simulated dermatitis herpetiformis The patient died one year after onset of the illness and autopsy revealed reticulum cell lympho sarcoma primary in the nasopharynx with metastases to the lymph nodes and the liver

appeared, particularly on the chest and upper half of the abdomen

Occasionally the intensely pruritic prurigo-like papules resemble dermatitis herpetiformis, as in the following cases

Bernstein (8) reported a 44 year old man who presented a dermatitis herpetiformis-like cutaneous eruption There was a polymorphous, macular, papular, vesicular eruption with large pigmented spots on the lower extremities, and a scattered pustular and papular eruption of the face Urticaria like lesions, of papular character, and some nondescript bluish red patches resembling Duhring's disease were present on the trunk Histologically, the picture was considered to be consistent with a diagnosis of a lymphosarcoma "id" Chargin (22) described a 51 year old man in whom the histologic diagnosis of a lymph node was lymphosarcoma He was given roentgenotherapy and after the fourth treatment he developed a cutaneous eruption on the forehead, neck, arms, and forearms, particularly on the extensor surfaces, and the dorsal aspects of the hands There were a few scattered lesions on the abdomen and buttocks, fairly numerous lesions on the extensor surfaces of the thighs and legs and numerous lesions on the dorsa of the feet The cervical and axillary lymph nodes, while still palpable, had decreased in size The cutaneous eruption was papular, the lesions varied from 'millet seed to pea' size, were reddish or of normal skin color, and severely pruritic Histologically, there was foci of inflammatory cells and spindle cells surrounding the blood vessels, but no evidence of lymphosarcoma in the skin

Cannon's (19 case 4) patient was a 71 year old woman who had numerous discrete, 'pea sized, red, puffy, edematous, excoriated cutaneous papules, particularly on the extensor surfaces of the extremities There were numerous purpuric spots, of "pin head' size, on the legs and on the lower outer third of the left leg there was a 'palm sized, hemorrhagic area having a scaly surface The left inguinal lymph nodes were the size of a 'fist," hard, nontender, and bound down to the underlying structures and were histologically lymphosarcoma All therapy

thema multiforme The condition was at first believed to be a drug reaction but two months later similar lesions recurred Five months later the lesions on the right side of the hard palate had become more marked and histologic examination showed a granuloma Three years after the onset of the mouth lesions she had a violaceous discoloration of nearly the entire top of the head most marked in the left parietal region There was decided alopecia and telangiectases with some crusting and a "pigeon egg" size cutaneous tumor was present in the right parietal region There was definite ptosis of both upper eyelids and a large tumor the size of a pigeon's egg" in the right submaxillary region Histologic examination of the skin tumor and lymph node disclosed lymphosarcoma

H E Miller (100 case 4) described a patient who had a recurrent toxic bullous cutaneous eruption of the lower extremities associated with lymphosarcoma At autopsy the clinical and pathological diagnoses were small cell lymphosarcoma A 39 year old man having erythema multiforme was reported by Connor (27) The lymphosarcoma began as a sero purulent nasal discharge and the right side of the nose became swollen He improved following roentgenotherapy but the process recurred five weeks later There was a perforating ulcer surrounded by granulations and having a purulent exudate in the midline of the hard palate The patient was at first presented as an example of mycosis fungoides "d emblee" This again emphasizes the fact that mycosis fungoides "d emblee" is lymphosarcoma There were also toxic nodular cutaneous lesions of an erythematous type which resembled erythema nodosum present on the thigh Histologic examination of these lesions revealed "chronic inflammatory tissue At autopsy the disease was found to be generalized with lesions in the skin lungs left testicle and lymph nodes The primary lesion had occurred in the mucosa of the nose Histologically the process was lymphosarcoma D Arbela and Bracaloni (31) also described a morbilliform cutaneous eruption

A 65 year old Negro whose presenting symptom was a generalized lichenoid intensely pruritic cutaneous eruption was



18 Prurigo like papules of the face with proptosis of right eyeball due to lymphosarcoma



19 Prurigo like papules of the legs

Erythema Multiforme The initial symptom in a 62 year old woman described by Oliver and Kerrigan (106) was an erythema multiforme like lesion in the mouth She had a pain ful tender lesion on the upper alveolar ridge on the left side and a similar lesion on the right side of the palate Both lesions were dark bluish red and had the appearance of ery

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described by Lamb and Stout (85). He had numerous, large cervical lymph nodes A diagnosis of lichenified eczema and "lymphoblastoma" was made and, because the blood serologic (Wassermann) reaction was positive, arsenotherapy was begun The pruritus was somewhat relieved but the lymphadenopathy did not recede with arsenotherapy The skin, which had lost its elasticity, appeared to be "hanging on the body," and had a "leathery" texture with bulging of the body folds The submaxillary, anterior and posterior cervical lymph nodes were enlarged and hard, while the axillary and inguinal nodes were slightly enlarged The skin of the legs appeared lichenoid, and the arms and back were studded with lichenoid papules with numerous white scars and excoriations The histologic diagnosis was subleukemic reticulosis, reticulum cell sarcoma type

Wile (140a) presented a 25 year old man who developed a pruritic cutaneous eruption on the hands 18 months previously which spread slowly to involve the forearms, groins and face Swelling of the groin, which had been present for about five years, was believed to be a hernia One type of eruption present on the face, groins, neck and forearms, was composed of confluent plaques, formerly vesicular which became considerably crusted, weeping, scaling and apparently pruritic Another type of eruption, confined to the genital region, consisted of several elevated plaques, of quarter dollar" size, which were dull, inflammatory and slightly condylomatous There was a generalized lymphadenopathy more marked in the right inguinal region where it presented an orange-red tumescence, apparently composed of several smaller tumors All the lymph nodes were discrete, not especially tender and moderately firm Histologic examination of an inguinal lymph node revealed lymphosarcoma One of Symmers (132c case 6) patients was a 13 year old boy who presented numerous petechial hemorrhages in the skin and conjunctiva, together with crusted blood about the gums

Herpes Zoster. When associated with lymphosarcoma, the mechanism of herpes zoster is due, as in Hodgkin's disease, to

compression by the new growth which results in stimulation of the virus and the development of zoster along the distribution of the affected nerve

The first pathologic investigation of the condition of the spinal ganglia in herpes zoster complicating this group of diseases was made by Head and Campbell (67) in 1900 They reported one case of lymphosarcoma complicated by herpes zoster of the fourth dorsal area At autopsy the upper seven spinal ganglia and posterior roots of the affected side were found to be involved by new growth Of the spinal ganglia only the fourth showed inflammatory and degenerative changes They showed that herpes zoster was caused by the new growth surrounding and compressing the ganglion and since their study Fahr (45) and Morton (103) have reported finding degenerative changes in the spinal ganglia corresponding to the peripheral area in which herpes zoster occurred in cases of lymphosarcoma Freund (56) Fischl (50) and Bluefarb (13a) have reported this same association in cases of leukemia

Craver and Haagensen (29d) reported 59 patients with lymphosarcoma three (7 per cent) of whom developed herpes zoster The first patient a 57 year old man had herpes zoster of the ninth left dorsal nerve The second a 53 year old man had herpes zoster along the ninth and tenth right dorsal nerves and the third patient a 31 year old man had herpes zoster along the tenth right dorsal nerve All three patients had previously received deep roentgenotherapy Wohlwill (143) performed autopsy examinations on six cases of herpes zoster and his sixth case demonstrated lymphosarcomatous metastases which were the cause of the zoster Kaposi's (78) case was probably associated with the ingestion of arsenic This patient who had lymphosarcoma developed a few cutaneous tumors which were treated with subcutaneous injections of arsenic after which the herpes zoster appeared A marked increase in the number of tumors occurred later and further arsenotherapy did not cause recurrence of the zoster Davison and Michaels (33 case 2) described a 40 year old man who had lymphosarcomatous in

volvement of the posterior nerve roots which resulted in herpes zoster over the region of the fourth and fifth ribs

Herpes zoster associated with mycosis fungoides "d'emblee" was reported by Semon (123) This 64 year old man developed herpes zoster on the anterior surface of the arm, abdomen, and right side of the neck, which became generalized Histologic examination of the tumors revealed mycosis fungoides "d'emblee" The tumors disappeared two weeks after a single roentgen ray treatment Videbaek (137) reported a patient with lymphosarcoma of six years' duration who, shortly before death, developed generalized herpes zoster Santos-Silva (120) reported a case of leukosarcoma accompanied by generalized herpes zoster which subsequently developed into lymphocytic leukemia

Exfoliative Dermatitis. Exfoliative dermatitis may occur in association with chronic lymphocytic leukemia and Hodgkin's disease, as well as with lymphosarcoma Clinically, the erythrodermatous type is indistinguishable from that present in leukemia or Hodgkin's disease Exfoliative dermatitis was described in association with Brill Symmers disease by Combes and Bluefarb (26c)

Netherton and Curtis (104) described a 29 year old man who, at 18 years of age first had exfoliative dermatitis, which responded to treatment At 25 years of age he again developed exfoliative dermatitis with lymphosarcomatous nodules A 52 year old man reported by Keim (60a), presented a generalized cutaneous eruption There was a diffuse hyperpigmentation with slight scaling of the face and at first glance, the trunk, thighs and arms presented a picture of an extensive exfoliative dermatitis consisting of evident thickening branny desquamation, and fine wrinkling and fissuring Closer examination disclosed a generalized mottled pigmentation of the trunk, with atrophy and telangiectasia suggesting a chronic radiodermatitis No definite localized infiltrates were apparent, but generalized lymphadenopathy was present In the left axilla there were three definite areas of ulceration there was a small "bean" sized ulcerative nodule with a clean base just above the nipple,

a discharging sinus from a 1 65 by 3 8 cm tumescence in the axillary fold and just posteriorly and more exactly in the axilla was an area of ulceration the size of a "large kidney bean which consisted of an irregularly shaped mass occupying nearly the entire left axilla The clinical pictures strongly suggested poikiloderma atrophicans vasculare Keim stated that the similarity of observations in this patient to the examples of poikiloderma atrophicans vasculare described by Lane (86) and Ormsby (107a) "was so striking that this case should be regarded as an example of the Jacobi type of this rare condition" Histologically however the infiltration of the neoplasm consisting of a large round cell lymphosarcoma type with abundant stroma throughout the skin and lungs as well as in all the lymph nodes of the body with localization in the lymphoid tissue would place this case in the lymphoma group of diseases Of the three recorded autopsies of poikiloderma atrophicans vasculare (Keim 80a Lane 86 Ormsby 107a) two revealed lymphosarcoma and one Hodgkin s disease

Case Report A 78 year old man first developed areas of cutaneous erythema three weeks previously These areas soon spread until the entire cutaneous surface was red thickened dry scaling and moderately pruritic Simultaneously the legs and feet became edematous and painful The palms were moderately thickened and lichenified and he had inguinal and axillary lymphadenopathy The histologic examination of the skin revealed some surface hyperkeratosis and parakeratosis and a perivascular round cell infiltration at the corium The majority of the cells were lymphocytes but there were also numerous mononuclears and an occasional plasma cell and eosinophil were noted The diagnosis was lymphosarcoma

Case Report A 56 year old Negro first developed pruritus of the dorsum of the hands one year previously which was followed by a papular cutaneous eruption Generalized pruritus then developed and the entire cutaneous surface became thickened and scaly In addition to the generalized exfoliative dermatitis he had enlargement of all the superficial lymph nodes and hepatomegaly The hemogram revealed 94 per cent

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20 Exfoliative dermatitis
21 Purura of the chest and face

hemoglobin and 16 300 white blood cells per cu mm with 36 per cent polymorphonuclears 5 per cent band forms, 2 per cent eosinophils, 1 per cent basophils and 55 per cent lymphocytes Atypical lymphocytes and 3 lymphoblasts were also noted

Purpura. Purpura occasionally occurs in association with lymphosarcoma and has the same mechanism and significance as purpura associated with Hodgkin's disease

Pigmentation The mechanism of pigmentation in lymphosarcoma is similar to that in Hodgkins disease Pigmentation of the skin (Addisons disease), associated with lymphosarcoma, involving particularly the retroperitoneal lymph nodes of the solar plexus region was reported by Warthin *et al* (139) The cutaneous pigmentation is of the type usually present in Addison's disease since extreme pigmentation, as found in this case, is practically always Addisonian despite the fact that there was no pigmentation of the mucous membranes, a feature

not always present The varying skin colors and the distribution of skin pigment are characteristic and the excess of corium pigment over that of the rete is found in the majority of cases of Addison's disease with marked pigmentation They believed one important point not previously recorded to be the pigmentation with melanin of that portion of the subcutaneous lymph nodes lying next to the skin All the lymph nodes so located presented on their flattened cutaneous aspects a deep black band from 1 to 1.5 mms in thickness due to the presence of large pigmented branching reticuloendothelial cells in the stroma around the blood vessels of the lymph nodes This pigment is melanin and apparently identical with that present in the skin The presence of melanin like pigment in the lymph nodes in Addison's disease has been explained as a pigment transportation from the skin to the lymph nodes Warthin *et al* concluded that their case was one of Addison's disease due to pressure atrophy of the chromaffin tissues of the abdominal sympathetic and adrenal glands produced by a lymphosarcoma primary in the retroperitoneal lymph nodes

Acanthosis nigricans has also been described in association with lymphosarcoma

Trophic Changes Glazebrook and Tomaszewski (61) described ichthyosiform atrophy of the skin in lymphosarcoma The patient a 44 year old man first developed right axillary lymphadenopathy Marked cutaneous pigmentation had occurred during the previous five years He presented a diffuse generalized brown pigmentation having the distribution and appearance of melanin but the mucosa were not involved The skin was universally dry and atrophic with a tendency to hyperkeratosis on the soles but there was no evidence of infiltration or inflammation The nails appeared uneven and transversely ridged Following hospitalization the skin became more dry and scaly and flaked in sheets while the hands cracked and oozed serum and a purulent conjunctivitis and a tendency toward ectropion appeared However definite improvement occurred during the sixth week when the skin became softer and less flaky and the eye condition improved

This improvement coincided with a decrease in body temperature and a rise in the plasma vitamin A concentration to 50 international units per 100 cc The patient s general condition was poor however and he soon died During the last week of illness the cutaneous pigmentation increased greatly over



22 Acanthosis nigricans (Geriatrics Bluefarb Sept 1956) *and* (*A M A Arch Dermat* Bluefarb (Feb) 1956)

the abdomen Glazebrook and Tomaszewski believed that the cutaneous changes in this case were due to a severe disturbance of hepatic function as revealed by laboratory studies It is known that hepatic dysfunction may result in upsets in vitamin A metabolism such as was present in this case Treatment with large doses of vitamin A were not effective However the basic disease process was progressive and vitamin A therapy failed to restore the plasma concentration even to a low normal level The plasma vitamin A concentration per

sisted at a low level and they believed that the damaged liver was "holding back vitamin A from the blood stream

Dermatitis nodularis necrotica as a cutaneous manifestation of a chronic systemic disease was described by Nieman and Wise (105) Autopsy revealed lymphosarcoma (reticulum cell type) of the thyroid gland stomach lymph nodes mesentery and skin The cutaneous eruption began as hemorrhagic papules and petechiae and later ulceration and healing with scarring occurred

Edema and swelling of both hands and ulceration of the dorsum of the right hand was described by Beerman and McGuire (5) This 62 year old man had shown a violent reaction to smallpox vaccine We have observed a patient who had marked edema of one leg due to obstruction of the lymphatics by lymphosarcomatous lymph nodes

B *Oral Lesions*

There are reports of lymphosarcomatous involvement of the tonsil tongue and hard palate

Tonsil Lymphosarcoma of the tonsil is rare according to Davis (32) who found reports of only 14 cases during a 25 year period Black (11) briefly mentioned seven cases six of which appeared to be of this type

Davis (32) believed there are three clinical types of lymphosarcoma of the tonsil The first and most common type is a sudden and rapid enlargement of one tonsil with an equally rapid enlargement of the corresponding lymph nodes of the neck occurring in persons of 40 or more years of age The tonsil is soft friable bleeds freely and the capsule is almost absent making enucleation difficult The histology of the tonsil is sometimes reported to be normal but within a few weeks the cervical lymph nodes increase in size and lymphoid nodules appear in the tonsillar fossa quickly forming a tumor Further careful search of the histologic section of the tonsil reveals evidence of lymphosarcoma Histologic study of a section of the tonsil and not a small portion of it is essential according to Davis who *described eight* cases of



23 Edema of the leg due to lymphosarcoma of the lymph nodes

this type He also reported four cases of the second type which closely resembled Vincent's angina at the onset The ulceration, at first superficial and confined to the tonsil area, later became very deep and extended to the surrounding structures The patients were about 40 years of age and gave a history of tonsillitis some weeks before the ulceration occurred Cervical lymphadenopathy was slight and not a distinctive feature The breath was foul Histologic examination of a sufficiently large piece of the floor of the ulcer revealed reticulum cell lymphosarcoma The diagnosis was doubtful for

some time and all usual treatment including intravenous salvarsan was ineffective. Unless radium therapy is instituted the patient soon dies sometimes with severe hemorrhage according to Davis. He believed it to be highly probable that this second type begins as the first type but the growth ulcerates more quickly before tumor formation is apparent. In two of his cases the ulceration occurred in both tonsils. It was also suggested that the growth spreads deeply in the tissues and then becomes ulcerated. He described two cases of the third type having a mass of enlarged lymph nodes in the neck. It was difficult to find the primary growth but this became evident later. Lymphosarcoma of the nasopharynx may resemble lymphosarcoma of the tonsil, but in the former case the lymphatic nodes at the angle of the jaw on both sides were enlarged although the primary growth was hidden for some time. Lymphosarcoma of the tonsil may resemble Hodgkin's disease and it is only when secondary growths occur that the true diagnosis is obtained. All patients with lymphosarcoma observed by Davis died within 18 months after the appearance of the first symptoms. A few patients received radium therapy the results of which appeared to be miraculous at first. The primary growths and lymph nodes rapidly disappeared but within a year the patients died of secondary growths in the chest or abdomen. Lymphosarcoma is well known to be very radiosensitive so that the earliest possible diagnosis and early radium therapy should be successful he concluded.

Lymphosarcoma of the tonsil occurring in a seven year old boy was reported by Chappell (21). Van Voorthuysen (136) stated that irradiation of a lymphosarcomatous tonsil must be followed by complete enucleation since recurrence is likely to occur. He reported a 60 year old Chinese patient who had a large ulcer on the right tonsil which was histologically lymphosarcoma. A "cure" was obtained with irradiation, surgery and further irradiation. A case of lymphosarcoma of the tonsil was reported by Caccialupi (17). Riehl (116) described involvement of the skin, lymph nodes, spleen and

bone marrow in a 48 year old patient who had definite evidence of involvement of the tonsils and pharyngeal wall

Jackson *et al* (75b) stated that malignant lymphoma of the tonsil occurs with sufficient frequency to merit careful attention and study particularly since it is apt to run a rapidly fatal course Although the initial symptoms are rather uniform it is essential to suspect the serious nature of the condition They tabulated 236 hospital admissions of malignant disease of the tonsil which occurred over a 15 year period Of these 28 (11 8 per cent) were proved to be some type of malignant growth The most prominent initial symptoms were persistent sore throat swelling within the throat and enlargement of the cervical lymph nodes They suggested that these patients be treated as if they had carcinoma of the tonsil that is with very heavy initial radiation with comparable doses for recurrences"

Tongue One of Cutler's (30 case 1) patients had a 2 by 2 cm ulcerative lesion on the right side of the base of the tongue which was histologically lymphosarcoma Another patient (case 2) presented a mass pushing the anterior pillar forward and extending downward toward the epiglottis in the left tonsillar fossa in addition to numerous cutaneous and subcutaneous scalp nodules Four patients (cases 3 4 5 and 6) presented oral involvement He commented that lymphosarcoma associated with lesions of the tonsil or tongue may be unilateral or bilateral It frequently grows to large dimensions and is seen as a bulky tumor which ulcerates late in the disease The cervical lymph nodes are almost always involved in the early stage of the disease In rare cases the disease is localized to the tonsil and the regional lymphatic nodes and adequate irradiation results in the disappearance of the lesions the patient sometimes remaining well for prolonged periods

Case Report A middle aged man presented lymphosarcoma involving the base of the tongue and the left cervical and left axillary lymph nodes

Autopsy revealed a 5 by 3 by 3 cm elevated red tumor mass having a smooth surface involving the base of the tongue and the dorsal surface just above the epiglottis Histologic



24 Lymphosarcoma involving base of the tongue

studies revealed this lesion to be composed of soft cellular grey tumor tissue extending into the musculature of the tongue A few small petechial hemorrhages were present in the tumor The lateral left wall of the pharynx was markedly thickened and consisted of greyish white fairly firm tumor tissue one cm in thickness Histologic examination revealed the cervical lymph nodes to be fairly firm greyish white in color and homogeneous

Hard Palate Primary lymphosarcoma of the hard palate appears to be extremely rare One patient reported by Freedman (55) responded favorably to roentgenotherapy He reviewed the literature from 1893 when Kundrat (84) established lymphosarcoma as a disease entity to 1940 and could find only one other case of primary lymphosarcoma limited to the hard palate This case was reported by Chaton (23) Although there have been numerous instances of lymphosarcoma of the hard palate all were secondary involvement by contiguity from lesions of neighboring structures

The rarity of primary lymphosarcoma of the hard palate according to Freedman (55) suggests the *following explana*





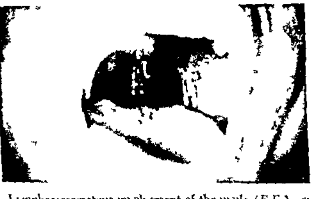
25 Lymphosarcomatous involvement of the hard palate (*A M A Arch Dermat* Bluefarb (Feb) 1956)

26 Lymphosarcomatous involvement of the hard palate

tion By definition, lymphosarcoma is a malignant neoplasm arising from lymphoid tissue While the structure of the oral and pharyngeal cavities, such as the posterior nasopharyngeal wall the fauces the adenoids, the tonsils, and the soft palate, are relatively rich in lymphoid tissue, the hard palate is singularly free of this tissue Quoting Gray's (64) Anatomy textbook The palate is covered by a dense structure formed by the periosteum and the mucous membranes of the mouth, which are intimately adherent On either side and in front of the raphe the mucous membrane is thick, pale in color and corrugated behind it is thin, smooth and deeper color it is covered with stratified squamous epithelium and furnished with numerous palatal glands which lie between the mucous membrane and the surface of the bone' Schumacher (122) in a detailed histologic description of the hard palate, also made no mention of the presence of lymphoid tissue Therefore, the paucity of lymphoid tissue in the hard palate explains the rarity of its occurrence at this site according to Freedman (55)

Keim (80) case 4) described a 72 year old man who had an irregular area of ulceration at the junction of the hard and soft

palates just to the left of the midline The border of the ulcer was elevated and slightly rolled back while the base was necrotic and bled easily on pressure The lesion was firm and painful to palpation On the upper right alveolar margin was an ulcerated area with characteristics similar to those of the lesion on the palate

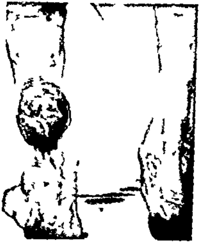


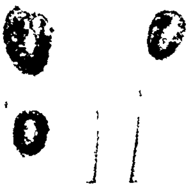
27 Lymphosarcomatous involvement of the uvula (E E N and T *Monthly* Bluefarb and Rodin (June) 1952)

Case Report A 20 year old Mexican man first developed a tumor on the left leg which was histologically reported to be fibrosarcoma Nine months later purpuric streaks which apparently occurred spontaneously developed on the body Within the preceding six weeks infiltrated plaques had appeared on the cheeks On examination there were bluish red raised moderately infiltrated plaques on the upper half of each cheek and involvement of the uvula There were numerous linear streaks composed of hemorrhages on the chest and sides of the trunk There appeared to be some atrophy of the interosseous muscles of the right hand which many physicians had suspected to be leprosy On histologic examination the corium was found to be infiltrated with a large number of immature cells of the lymphocytic type A diagnosis of lymphosarcoma was established at autopsy

C Specific Lesions

McCarthy (93) described the specific nodular cutaneous lesions of lymphosarcoma as one or several "pea to hazel nut" sized firm round or oval bluish red elastic tumors at the onset They are not painful on palpation are freely movable over the underlying structures and appear to arise in the skin of subcutaneous tissue The tumors increase rapidly in size to that of an egg or an "apple and increase in number





28 Lymphosarcomatous nodules and tumors (*A M A Arch Dermat* Bluefarb (Feb) 1956)

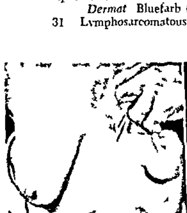
29 Lymphosarcomatous nodules and tumors (*A M A Arch Dermat* Bluefarb (Feb) 1956)

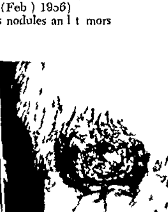
Case Report A 43 year old man first developed several furuncles involving the right axilla nape of the neck behind the left ear and on the chest following removal of a body cast Three months later he was admitted to the hospital at which time he had a carbuncle on the neck and furunculosis Therapy consisted of the administration of antibiotics and surgical incision of the lesions Following drainage of these lesions he developed a large round sharply marginated elevated infiltrated cutaneous lesion on the nape of the neck which did not heal The hemogram revealed 44 per cent hemoglobin 2,520 000 red blood cells and 12 950 white blood cells per cu mm with 48





30 Lymphosarcomatous nodules and tumors (*A M A Arch Dermat* Bluefarb (Feb) 1956)
31 Lymphosarcomatous nodules and tumors





32A Lymphosarcomatous nodules and tumors
32B Lymphosarcoma of the neck (case report)

C Specific Lesions

McCarthy (93) described the specific nodular cutaneous lesions of lymphosarcoma as one or several pea to hazel nut sized firm round or oval bluish red elastic tumors at the onset They are not painful on palpation are freely movable over the underlying structures and appear to arise in the skin of subcutaneous tissue The tumors increase rapidly in size to that of an egg or an "apple and increase in number





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33 Ulcerated lymphosarcomatous nodules (A M A Arch Dermat Blefarb (Feb) 1956)

34 Ulcerated lymphosarcomatous nodules (A M A Arch Dermat Blefarb (Feb) 1956)

per cent polymorphonuclears, 6 per cent bands 1 per cent eosinophils, 43 per cent lymphocytes and 2 per cent monocytes. Biochemical examination of the blood disclosed 156 mg./100 cc glucose. Sternal bone marrow study was reported to show reticulum cell sarcoma with giant cells, "the possibility of metastatic carcinoma cells cannot be ruled out." Histologic examination of the cutaneous lesion revealed a picture compatible with lymphosarcoma cutis.

Metastatic cutaneous nodules were described by Epstein and MacEachern (42) as being firm, but not as hard as those present in carcinomas. The color varies from bright red to deep blue, depending upon their depth. Ulceration of the nodules, although not common, has been observed in lymphosarcoma.

The first patient described by Menne and Bitar (99) was a 74 year old man who suddenly developed cutaneous and subcutaneous nodules of widespread distribution without primary local manifestations in any one group of lymph nodes, either clinically or at autopsy. The original involvement of a group of lymph nodes may have been masked by the extensive involvement of the skin and subcutaneous tissues. At no time was there evidence of pruritus or pain of the nodules. The chief symptoms consisted of swelling of the face, orbit and ear, abdominal distress due to ascites, which was associated with pleural effusion and a terminal bronchopneumonia. Their second patient was a nine month old infant. They assumed that the primary lesion was in the vicinity of the right shoulder where a large mass had been removed for histologic study which proved to be lymphosarcoma.

Two cases of reticulum cell lymphosarcoma, in which there was emphasis on cutaneous touch smears, were reported by Feldaker *et al.* (47). Both patients had similar cutaneous eruptions consisting of generalized, discrete nodules. Both had definite spontaneous remissions of the disease following nitrogen mustard therapy. In the first patient the cutaneous lesions in nonirradiated regions underwent involution following roentgenotherapy to the involved cutaneous areas. In the second



36 Ulceration of the skin from extension of an involved cervical lymph node

amount of infiltration extended into the subcutis A 29 year old man reported by Netherton and Curtis (104) had lost considerable weight was pale and mildly cachectic He had a remittent pruritic eruption between the ages of six and 20 years and at 25 years of age he developed a nodule in the left axilla accompanied by recurrence of the pruritic eruption The nodule was histologically lymphosarcoma The cutaneous eruption gradually spread to the face trunk and thighs following roentgenotherapy He had scalp nodules of one years duration

A 67 year old man described by Director and Kern (36) developed a growth on the cheek six months previously Other tumors gradually appeared on the face until there were



35 Ulcerated lymphosarcomatous nodules

patient, there was no histologic evidence of "lymphoblastoma" in a previously involved cutaneous area following intravenous nitrogen mustard therapy The cutaneous and visceral lesions responded well to roentgenotherapy In both patients the peripheral blood and bone marrow studies were not diagnostic but cutaneous touch smears revealed distinctly immature cells which were also evident in paraffin sections

Ehrlich and Gerber (39) noted isolated metastases to the skin and direct extensions from underlying lymph nodes in two of 18 cases McCafferty and Machacek (92) described a patient who had lymphadenopathy for several years, subcutaneous nodules and hepatosplenomegaly Their second patient had slight lymphadenopathy and several, fairly large, protruberant, relatively soft reddish tumors having a slight

(140b) had "swellings in the left groin and of the skin The inguinal swelling had been incised and a sinus remained Histologic examination of a lymph node revealed lymphosarcoma His second patient a 59 year old man developed swelling of the left inguinal region which resulted in swelling of the entire leg There was a purplish red firm nodule on the lower left leg Histologically the inguinal lymph node showed lymphosarcoma

Combes (26a) first patient was a 61 year old man who first developed a "pea" sized painless cutaneous nodule in the right temporal region It increased to "hen s egg" size in one year and small cutaneous nodules appeared on the chest and back Histologic examination of the forehead lesion revealed lymphosarcoma The multiple tumors in this case bore a definite histological resemblance to mycosis fungoides "d em blee" His second patient a 58 year old man had a single painless slowly growing cutaneous nodule on the cheek over the malar bone Although this single nodule resembled Spiegler Fendt sarcoid the future course of the disease proved it to be lymphosarcoma Pautrier and Woringer (111) described a man in his twenties who had multiple cutaneous tumors which clinically resembled Darier Roussy sarcoid However histologic examination of a lesion from the abdominal wall and one from the hip revealed diffuse and circumscribed collections of lymphoblasts

Two instances of fixation of the lymph nodes in lymphosarcoma were noted by Symmers (132c) There was ulceration of the skin in one case a 58 year old man who had massive swelling and edema of the left hand and arm There were huge masses of lymph nodes firmly attached to the skin and underlying structures on both sides of the neck The skin on the left side of the neck behind and about the middle of the sternocleidomastoid muscle was eroded giving rise to a 5 cm irregularly rounded ulcer which had sloping edges and a reddish granular base Cutler (30 case 16) described a 44 year old man who had nodular cutaneous masses over the anterior chest wall for five months followed by similar lesions in

ten nontender, elevated, well defined, reddish brown, rounded tumors from 2 to 10 cms in diameter There were some telangiectases overlaying the larger lesions Both legs showed brownish pigmentation and chronic dermatitis, and there were several large ulcers on the lower right leg Two months later he had developed scrotal masses Although the lymph nodes were not primarily affected, the inguinal nodes later became secondarily involved by extension from the testicular lesions The patient died one year after onset of the disease Histologically, the lesions removed early in the disease resembled Spiegler-Fendt sarcoid but later specimens proved the tumor to be a reticulum cell lymphosarcoma A tumor of the left thigh showed the epidermis to be thinned and compressed by a very dense massive cellular infiltrate which filled the entire corium and invaded the hypoderm, infiltrating the fat lobules The cells of the infiltrate consisted almost entirely of reticulum cells They had no clearly defined cytoplasm, and the nuclei were of the histiocytic type, vesicular but deep staining, large, and varied in size and shape, and contained one to three nucleoli Mitotic figures and degenerated forms were numerous, with signs of growth predominating A few lymphocytes and an occasional neutrophil were scattered about The general appearance was that of an actively growing tumor, and the picture resembled that of the infiltrate of the testes

A 40 year old man who had developed a purplish, elevated nodular, flat infiltration at the site of a previously excised lesion on the wrist and two enlarged lymph nodes above the elbow, was presented by Rothwell (118) The lesion was lymphosarcoma on histologic examination Fox's (53) patient, a 43 year old man, presented numerous tumors on the face, scalp chest, axillae, inguinal regions, back and thighs These tumors were from "split pea to palm size elevated from 0 3 to 2 5 cm, and the largest, on the cheek measured 8 8 cms There were various sized tumors on most of the anterior two thirds of the scalp These tumors involved the overlying skin and were freely movable on the deeper parts The histologic diagnosis was lymphosarcoma A 15 year old boy described by Wile

were of "cherry" size Some mature growths were "thimble shaped" dark purple under a smooth epiderm and contained a dark bloody fluid on aspiration Some nodules showed ulceration secondary infection and many were undergoing involution Sites of lesions which had disappeared were of a dark brown color The lesions underwent resolution with roentgenotherapy but new ones appeared rapidly in areas not previously involved and the face scalp and neck became involved in the process

A 68 year old man described by McNamara and Henneger (95) developed a painless nodule in the subcutaneous tissues just below the left parotid gland Histologic examination revealed lymphosarcoma and roentgenotherapy caused the lesions to disappear Fourteen months later a generalized cutaneous eruption and an ulcer of the right cheek had appeared There were numerous bluish red slightly elevated nodules over the entire body but most marked on the scalp face and trunk The overlying skin was smooth less pliable than normal with the deepest color in the center of the lesion and fading perceptibly into the surrounding skin The lesions 1 to 5 cms in diameter tended to become confluent over the chest while the largest lesion on the right cheek resembled an indolent boil with dilated veins at the periphery and blood covering the center of the lesion There was slight cervical axillary and inguinal lymphadenopathy and the nodes were discrete and freely movable

Langmead and Heggs (87) described a 54 year old man who had developed swelling in both preauricular regions one month previously followed by involvement of the axillary and inguinal regions The lymph nodes in the neck and popliteal spaces were also enlarged The histologic diagnosis was lymphosarcoma Cutaneous nodules which appeared during the next few weeks resembled the enlarged lymph nodes histologically but had fewer mitoses The nodules regressed following roentgenotherapy A 26 year old man reported by Matheson (96) had multiple subcutaneous nodules Histologic examination of a cervical lymph node revealed lymphosarcoma Three

both axillae and groins Autopsy revealed a severe degree of jaundice, cutaneous and subcutaneous tumor nodules, and invasion of the lymph nodes in the neck, axilla, groins, mediastinum, and retroperitoneal areas In the region of the thymus gland there was a discrete tumor composed of round and polyhedral cells, which were growing diffusely, with numerous mitoses This case is an example of rapid primary response to irradiation followed by prompt recurrence, in a patient in whom the disease was widespread throughout the body

Ormsby (107b) described a 33 year old man who had an indurated penile lesion, proved to be lymphosarcoma, which became generalized by metastatic involvement of the abdominal and thoracic regions and terminated fatally in one year A cutaneous eruption of pigmented macules of 'pea to half-dollar" size involved the trunk These lesions were contiguous and produced a mottled effect The arms and legs were similarly involved but were less pigmented There were large areas of telangiectasia and atrophy simulating healed radiodermatitis, on the thighs

The 75 year old man described by Sweitzer *et al* (131), had a purple red cutaneous plaque in the right preauricular region of four weeks duration Histologic examination indicated lymphosarcoma and roentgenotherapy was given One year later he had developed scattered purplish red plaques on the head and all parts of the body, except the hands and feet These hemorrhagic, tender indurated tumors, from 1 to 10 cms in diameter, were most marked on the thighs Fraser (54) reported a 25 year old woman who had numerous tumor-like lesions, of "pinhead to cherry size on the trunk and extremities The majority of the lesions were discrete, but some larger nodules tended to become confluent appearing as lobulated masses, particularly on the buttocks and upper, inner portions of the thighs Various stages of development were evident the recent lesions were pinpoint to pinhead' size slightly elevated, discrete, reddish papules surrounded by a zone of erythema, the slightly larger nodules were of "millet seed to pea' size, while the fully developed dark purplish red tumors

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months later, numerous discrete, painless cutaneous nodules were widely distributed on the anterior abdominal and thoracic walls The largest and most numerous lesions were toward the midline These lesions enlarged slowly and varied from "miliary dimensions to cherry" size They were freely movable and the overlying skin was not reddened, tender or puckered

Senear and Schorr (124) presented a 23 year old Negress who had subcutaneous nodules on the body, most prominent on the back, upper chest and breasts Histologic examination of a lymph node and a cutaneous nodule revealed lymphosarcoma A 56 year old man who first noted a 'lump" under the jaw was described by Bingham and Quarrier (10) Two weeks later he developed generalized malaise, weakness, constipation *with ribbon like stools, inguinal lymphadenopathy, and cutaneous* nodules The nodules and lymphadenopathy continued to progress until his death two and one half months later At autopsy the skin was studded with firm, elevated nodules, up to 3 cms in size, which were skin colored, red or non pigmented The overlying epidermis was tensely stretched, giving a glistening appearance On cut section the nodules showed firm greyish white tissue covered by a thin layer of epidermis suggesting an intracutaneous position There was marked enlargement of the cervical, axillary and inguinal lymph nodes, some measuring 6 cms in diameter A 36 year old woman who developed a small cutaneous tumor on the left arm and one near the left breast was reported by Mayer and Wolfram (98) Nine months later, a maculo papular exanthem appeared on the face and arms which soon increased to large partly ulcerated nodules involving the entire skin and some visible mucosa She died seven months later and histologic studies at autopsy showed a general overgrowth of reticulum cells of tumor like character, especially in the skin and mucosa The tumors not sharply circumscribed, infiltrated the normal tissue There was no evidence of a primary tumor and no definite metastasis The endothelial cells showed no proliferation with the exception of Kupffer cells, and there were no monocytes in the infiltrate

Poble and Golper (112) reported a 71 year old man who had developed a painless "lump" of "hickory nut" size on the left side of the neck two years before. One year later a similar growth appeared on the right side of the neck and shortly thereafter a similarly sized nodule was noted on the left buttock. At this time he developed progressive weakness, the lesions on the buttock increased in size and tenderness and assumed a purple color. The cervical lymph nodes were large matted masses which extended down to the supraclavicular region on the right side. The left inguinal lymph nodes were enlarged to 3 cms but not matted and there were small discrete lymph nodes in the right inguinal region and in both axillae. There was a firm rounded 8 cm mass which was raised 3 cms above the skin surface on the upper inner left buttock. This dusky red lesion was apparently highly vascular. The mass, adherent to the underlying structures, was tender only on marked pressure. Histologic examination revealed lymphosarcoma.

Gangrene of the face produced by lymphosarcoma was described by Shebesta (125). The patient, a 33 year old man, had a swelling on the nose which was accompanied by a profuse foul smelling watery discharge. A 67 year old woman in whom lymphosarcoma was apparently localized to the eye lids and conjunctiva was reported by Levitt (89). The correct diagnosis was made by histologic examination. Heath (68) reviewed the general subject of ocular lymphomas as to incidence, clinical classification and pathologic structure. A case of lymphosarcoma of the eyelid which terminated fatally in 40 days was reported by Stansbury (127) who discussed all aspects of this subject. A woman who developed three distinctly different tumors during her lifetime was described by Hynes and Wintrup (72). First, a papillary cystadenoma of the ovary occurred, then a squamous cell carcinoma of the skin and finally lymphosarcoma of the skin. One of H. E. Miller's (100, case 3) patients, a 56 year old woman, had a foul smelling ulcerated mass the size of an "orange" in the right groin. The initial lesion on the hip was considered to

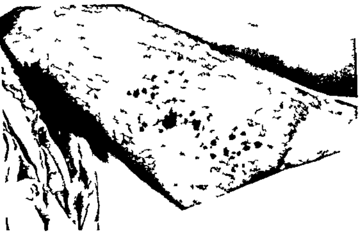
be mycosis fungoides d emblee However the autopsy diagnosis was lymphosarcoma

Case Report A 57 year old man complained of difficulty in swallowing and breathing weakness and loss of weight He had a large mass involving the right subparotid region and enlargement of the anterior cervical lymph nodes There was a solid mass 5 by 5 cms in size formed by the left mandible sternocleidomastoid muscle and the submaxillary lymph nodes Both the axillary and inguinal lymph nodes were enlarged bilaterally Histologic examination of the lymph nodes revealed lymphosarcoma

He died three months later and autopsy revealed subcutaneous nodules averaging 1 5 cms in diameter over the chest and abdomen which were palpable and visible through the skin There were circumscribed nodules the largest 6 cms in diameter present on both sides of the neck

Case Report A 48 year old man had an illness of several years duration which had been diagnosed giant follicular lymphoblastoma Following deep roentgenotherapy he had felt well until six weeks before admission to the hospital when the abdomen became enlarged and a cutaneous nodule appeared on the face and one on the shoulder The lower extremities then became edematous and he developed tightness of the abdomen and back pain There was a flat 5 cm sized cutaneous nodule near the left ear and another 10 cms in size involved the left scapular region There was an indefinite flattened linear mass present at the angle of the right scapula Hemogram revealed 2 700 000 red blood cells and 6 300 white blood cells per cu mm with 72 per cent polymorphonuclears 24 per cent lymphocytes and 4 per cent eosinophils He failed to respond to further deep roentgenotherapy and died three months after admission to the hospital

At autopsy the skin was pale and there was some roentgen ray pigmentation over the lower abdomen and groins There were numerous 5 to 1 5 cm round elevated cutaneous nodules on the inner aspect of the right thigh which were freely movable The right supraclavicular lymph nodes were palpable The anatomical diagnosis including histologic findings was



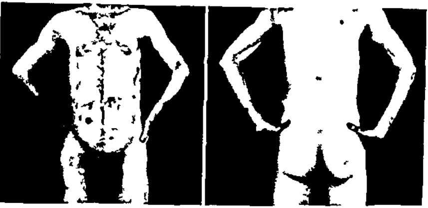
37 Cutaneous nodules on thigh

lymphosarcoma of the skin lymph nodes stomach and both kidneys

Histologic studies revealed Skin The skin appeared to be "flattened out" The rete pegs were almost absent There was an infiltration with tumor cells beneath the skin around the glands and in the subcutaneous fat Lymph Node There was complete destruction of the architecture and considerable necrosis The remainder revealed a tumor composed of the large hyperchromatic lymphocytes noted in other sections

Case Report A 31 year old man had numerous multiple subcutaneous nodules for four months preceding death The ante mortem histologic diagnosis was reticulum cell lymphosarcoma

At autopsy there were numerous 1 to 4 cm purplish blue subcutaneous nodules involving the face neck and extremities The nodules were superficially ulcerated in the right hypocondylar region and right lower quadrant of the abdomen There was cutaneous pigmentation of the left jaw and of both axilla Histologic studies revealed reticulum cell lymphosarcoma of the lungs pancreas adrenal glands myocardium stomach and skin



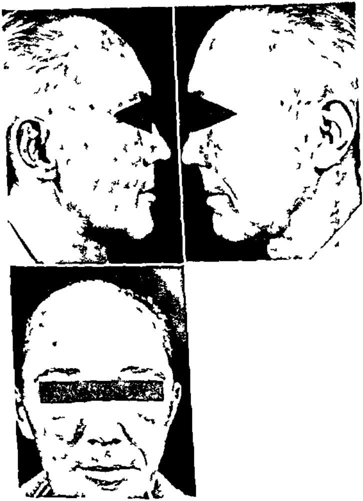
38 Multiple subcutaneous nodules of trunk and extremities

Case Report A 57 year old man first developed lymphadenopathy eight years previously which was reported to be giant follicular lymphoblastoma on histologic examination Four years later a cutaneous eruption appeared over both temporal areas which was diagnosed as lupus erythematosus and treated as such for the next four years when he developed a swelling of the left side of the jaw which was found to be lymphosarcoma on histologic examination He then developed paralysis of the left lateral rectus eye muscle which improved somewhat after deep roentgenotherapy to the temporal area

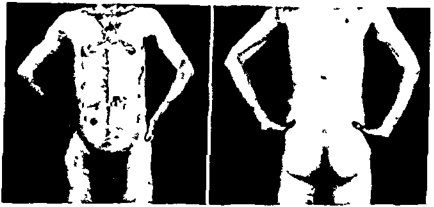
On examination there was a 3 by 1 cm red irregularly marginated cutaneous lesion in the right temple area and a 1 cm subcutaneous nodule in the right parietal region Two deep 2 cm masses were present in the left parotid area which were fixed to the underlying tissues but not attached to the skin A firm fixed slightly tender 2 to 3 cm mass involved the left supraclavicular region Histologic examination of the skin revealed lymphosarcoma

He died eight years after onset of the disease and autopsy disclosed lymphosarcoma with infiltration of all the retroperitoneal tissues adrenal glands and myocardium testicle and epicardium

Case Report A 45 year old man had marked edema of the face and inguinal cervical and axillary lymphadenopathy for several months He improved following roentgenotherapy but



39 Edema telangiectasia and nodules of the face



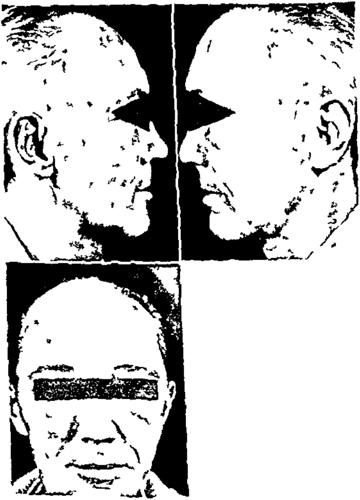
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was readmitted four months later At that time he had marked edema of the entire face and irregularly distributed telangiectasis on the forehead, zygoma, and intraocular areas, where numerous discrete, 1 to 2 cm cutaneous nodules resulted in a "woody" sensation on palpation and some edema Several firm nontender, freely movable nodules, of 2 cm size, were present above and below both orbits The diagnosis, at this time, was "follicular lymphoblastoma, probably Hodgkin's in type" However, the autopsy two and one half years later, revealed lymphosarcoma with infiltration

VIII.

LEUKOSARCOMA

THE PERIPHERAL blood picture frequently becomes leukemic in patients having lymphosarcoma This syndrome had been characterized as leukosarcoma by Sternberg (128), or as lymphosarcoma terminating in lymphocytic leukemia

Sternberg stated "Under this title (leukosarcomatosis) we separated from leukemic lymphadenosis a series of cases which, in their anatomical findings, had many points of contact with Kundrat's lymphosarcomatosis, but differed from that in certain respects, especially as regards the blood picture Lymphosarcomatosis runs its course, as a rule, without noteworthy blood changes Only exceptionally were cases observed in which there was a pronounced lymphemia But in the leukosarcomatosis there is in the blood a great increase of white blood cells, with a preponderance among them, sometimes exclusively, of large mononuclear structures with a relatively pale staining nucleus, which contains two or more vacuoles and with moderately copious non granular cytoplasm They give no oxidase reaction Sometimes the total white blood cell count is not raised and there is only a relative monocytosis At necropsy one finds a more or less widespread often universal, swelling of the lymphatic apparatus which in some places shows a pronounced malignant type of growth with unlimited invasion of neighboring tissues, as in lymphosarcomatosis Thus massive tumors arise whose site of election is the anterior mediastinum They could also arise in other parts e g, the tonsils, thymus, gut Changes in the areas of the lymphatic apparatus may be present, indistinguishable with the naked eye from those seen in lymphosarcoma Among skin changes mentioned in leukosarcomatosis *hemorrhage* take

first place" Ulcerations of the skin may also occur in leukosarcoma

There are also many reports of patients who received high voltage roentgenotherapy to a well localized lymphosarcoma and subsequently developed "leukemia" (leukosarcoma)

Among three cases of lymphosarcoma, described by Evans



40 Nodules of leukosarcoma with hemorrhages into the skin



41 Ulcer of the leg in leukosarcoma

and Leucutia (43) two had involvement of the mediastinum and one had lymphosarcomatosis localized to the lymphatic system All had normal peripheral blood pictures at the onset of the disease Following radiation therapy the disease apparently disappeared but extension to the bone marrow occurred in about three to six months and in two cases it also involved the subcutaneous tissues The picture of lymphocytic leukemia became manifest at this time This uniformity in the clinical extension of the process according to Evans and Leucutia indicates that the picture of lymphocytic leukemia is not merely a coincidence but is the result of a new localization of the lymphosarcoma Their first patient a 23 year old man had considerable mediastinal pressure symptoms which entirely cleared following deep roentgenotherapy Three months later metastases to the scalp occurred but also disappeared following roentgenotherapy Two months later he developed cutaneous manifestations and extension to the bone marrow At this time the picture of lymphocytic leukemia with marked progressive secondary anemia became manifest Post mortem examination revealed the only manifestation of lymphosarcoma to be present in the few cutaneous nodules and in the one nodule in the left auricle of the heart but there were marked histologic changes in the bone marrow which were the predominating feature of the disease The second patient a 21 year old man with generalized lymphosarcoma of the lymphatic system had pronounced cervical lymphadenopathy The tumors disappeared following deep roentgenotherapy Later cutaneous manifestations and bone marrow involvement occurred and the picture of lymphocytic leukemia with marked secondary anemia developed Post mortem examination revealed a few nodules in the retroperitoneal nodes and in the skin which were histologically lymphosarcoma The predominating changes were in the bone marrow Evans and Leucutia concluded that these cases proved without a doubt that lymphosarcoma transformed into lymphocytic leukemia as soon as the bone marrow became involved by the foci of lymphosarcoma The blood showed no increase of lymphocytes

as soon as the symptoms of the bone involvement became manifest, and the lymphocytosis was in direct relation to the extent of the bone marrow involvement Irradiation of the long bones produced an immediate decrease in the number of circulating lymphocytes Since lymphosarcoma transforms into lymphocytic leukemia as soon as the bone marrow becomes involved, the question arises as to whether or not chronic lymphocytic leukemia is a primary lymphosarcoma or a related process of the bone marrow Acute lymphocytic leukemia, or secondary lymphocytic leukemia, as observed after certain infections, form an entirely different group, and were not considered by Evans and Leucutia In several such cases of primary lymphocytic leukemia, they irradiated the long bones and the lymphocytes decreased at the same rate as in the two cases described here They acknowledged that, except for the identical radiosensitivity, there is no definite evidence in proving that typical chronic lymphocytic leukemia is a primary lymphosarcoma or related process of the bone marrow They believed, however that they 'have the problem one step nearer its solution by proving that lymphosarcoma is transformed into lymphatic leukemia as soon as the bone marrow becomes involved The picture from this moment on remains indistinguishable from the typical chronic lymphatic leukemia"

In reviewing the literature up to 1929 Flashman and Leopold (51) found 107 cases of leukosarcoma In 60 cases the primary site of the invasive tumor was in the mediastinum, in the skin in 11 cases in the eye or eyelid in 11 cases, and in the retroperitoneal and abdominal lymph nodes in six cases The pleura, peritoneum femur, breast dura and intestine were primary sites in two cases each whereas the skull, cervical lymph nodes, lymph nodes generally ribs, uterus, ovaries, tonsils, and prostate were represented as the primary sites in one case each

Goldsmith (62) reported a 65 year old man who complained of "lumps' on his face of two months duration These lesions were copper or plum colored infiltrated plaques 2 cms in diameter, involving chiefly the forehead and cheeks There

were numerous flat infiltrations on the lower extremities and a large fungating tumor which arose abruptly on the outer side of the left thigh had been present for two years The peripheral blood studies revealed 300,000 white blood cells per cu mm with 94 per cent lymphocytes Following roentgenotherapy to the face, thigh and spleen, some of the tumors on the face and extremities disappeared and did not recur, but the large tumor on the thigh, after short temporary improvement, grew rapidly At autopsy there was an extensive fungating, ulcerative cutaneous lesion extending over the greater portion of the outer and posterior aspect of the left thigh and encroaching onto the anterior aspect which, near the edges, appeared as an "exuberant cauliflower-like mass," raised above the skin surface Over the remainder of the thigh, especially on the inner aspect, were extensive raised, brawny and indurated swellings, some 17 8 by 12 7 cms, which, on section, had the same lobulated appearance as the infiltrated growth extending from the skin, which could be seen infiltrating down to the muscle fascia, but not to the muscle itself Histologic examination of a cutaneous nodule from the indurated area on the thigh showed an extensive monocytic infiltrate extending up to the epidermis and down to the subcutaneous fat which it was infiltrating Some parts of the tumor were markedly degenerated and there were abundant pyknotic nuclei with some polymorphonuclear leukocytes infiltrating, more particularly in the deeper areas Immediately beneath the epidermis the tumor cells were round or oval, seldom showing much cytoplasm and separated from each other by a structureless matrix, each cell lying quite discrete Some cells were "considerably larger and appear to have two or three nuclei The nuclei tends to be clear and pale with knotted reticulum definite nucleoli are not a feature of the cell"

Wile (140c) cited two illustrative cases The first patient, a young boy, had definite lymphosarcomatous nodules but little or no peripheral blood changes Later, however, severe hemorrhages into the skin and mucous membranes occurred, following which he developed a rapidly fatal fulminating type of

lymphocytic leukemia The second patient, an elderly man had multiple lymphosarcomatous nodules in the skin and lymph nodes with peripheral blood changes suggestive of leukemia

Ulcers of the legs rarely occur in lymphosarcoma *

* See Illustration 34

IX.

DIFFERENTIAL DIAGNOSIS

EXPERIENCE in clinical observation of the lymphomas teaches caution in attempting a differential diagnosis except by skilled histologic study. Clinically one can only hazard a guess which at times may have to include two, three or more possible diagnoses. There are no clinical features which without exception will permit differentiation between tuberculous lymphadenitis, Hodgkin's disease, lymphosarcoma, "aleukemic" lymphocytic leukemia, lymphoepithelioma, or even metastatic carcinoma of the lymph nodes. A therapeutic test dose of radiation is of little diagnostic value, as any of the above mentioned conditions may respond as readily as does lymphosarcoma.

Clinically, lymphosarcoma may be roughly divided into two groups according to Sugerbaker and Craver (130). These consist of those having a process obviously of monocentric origin presenting an asymmetrical lymphadenopathy involving mainly one to a few groups of lymph nodes, and those perhaps of multicentric origin presenting a fairly uniform symmetrical distribution of lymph nodes at once suggesting chronic lymphocytic leukemia. In the latter group a nonleukemic blood count necessitates histologic study of a lymph node to distinguish between Hodgkin's disease, rare cases of metastatic carcinoma, and especially between "aleukemic" leukemia and lymphosarcoma. Moreover, a leukemic blood picture does not necessarily exclude lymphosarcoma. There are also rare cases of generalized symmetrical tuberculous lymphadenitis and other generalized lymphadenopathies of inflammatory or metabolic origin to be differentiated according to Sugerbaker and Craver. Concerning the former more localized types they believed it may be said in general that lymphosarcoma tends



42 Nodules of dermatitis papillaris capillitii simulating lymphosarcomatous nodules (Courtesy Samuel J Zakon, M D)

to be more diffuse and more aggressive than the other processes mentioned In lymphosarcoma the lymph nodes tend to assume a rounded shape and a rubbery, firm consistency

The rare diffuse lymphosarcoma of the nasopharyngeal and oropharyngeal tonsillar ring presents a characteristic appearance, according to Sugerbaker and Craver (130) Lymphosarcoma of the tonsil, when fully developed, usually presents a bulky, smooth, spongy swelling in the tonsillar fossa with little or no ulceration until late stages of the disease In the

skin, lymphosarcoma characteristically causes raised, dusky red, "button like" plaques, similar to leukemia cutis

The presence of nodules in the scalp may occasionally present diagnostic difficulty between dermatitis papillaris capillitii and lymphosarcomatous nodules, as in the case presented by Zakon and Eirinberg (145)

X.

PROGNOSIS

FIVE FACTORS which influence the course of lymphosarcoma were listed by Sugarbaker and Craver (130). 1) Individual inherent qualities for growth and dissemination in the different tumors, i.e., many run a rapid course but a few may be very slow. Microscopic examination, they found, did not aid one in foretelling this, although in general the giant follicular lymphosarcomas run a less rapid course. 2) The extent of the disease at the time of admission. They found four of 21 patients who survived long had clinical evidence of disease in more than two contiguous areas. 3) The location of the primary lesion. The results were better when the primary site was in the head end of the body (23 per cent five year survivals and 15.4 per cent symptom free). They had no patients who survived long when the primary lesion was in the gastrointestinal tract, which is contrary to the experience of others. 4) Complicating leukemia. Of their series, 6.6 per cent of the patients had leukemia and all died. 5) The age of the patient. The average survival rate of the 0 to 29 year age group was only 11.3 months, while for later age groups it was more than twice that figure.

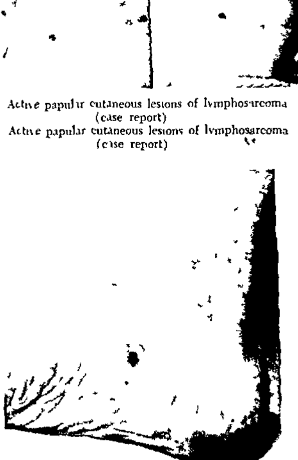
The five year survival rate appears to be better than average if the disease first manifests itself in the cervical, axillary and inguinal lymph nodes, the oral cavity and nasopharynx, the gastrointestinal tract and skin and orbit, and poorer than average if it begins in the retroperitoneal, mesenteric or mediastinal lymph nodes, of the spleen and thyroid gland, or if the condition is generalized, according to Stout (129). Persistence of the disease and later deaths, however, narrow the more favored group to those having involvement of the cervical and axillary lymph nodes, the mouth and nasopharynx and the gastrointesti-





43 Active papular cutaneous lesions of lymphosarcoma (case report)

44 Active papular cutaneous lesions of lymphosarcoma (case report)



45 Active papular cutaneous lesions of lymphosarcoma (case report)

nal tract He found the greatest number of cases to be of the reticulum cell type which had a survival rate well below the average Lymphocytic cell tumors were the next most frequent, with a survival rate of about one per cent above the average, while giant follicle tumors, with the smallest number of cases, showed a survival rate of about 12 percentage points above the average He believed, therefore, that the division of the tumors into histologic groups is one factor which may be used in statistical prognosis In his opinion, there are some

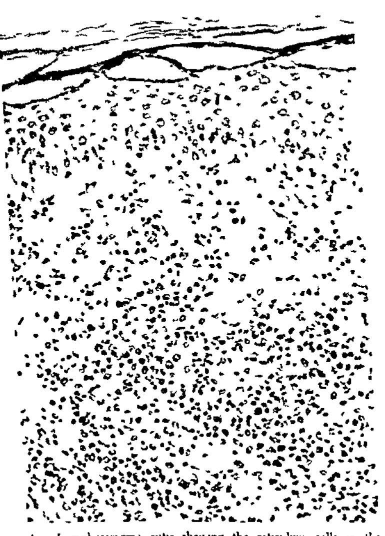


46 Scarring or healing phase of lymphosarcoma (case report)

factors which may be considered in the prognosis Giant

is over 40 years of age Cases associated with leukemia are always fatal

A patient who had spontaneous healing of the cutaneous lesions of lymphosarcoma was presented by Bluefarb, *et al* (13b)



1 Lymphosarcoma cutis showing the reticulum cells in the cutis many undergoing mitosis (case report)

Case Report A 56 year old woman first developed an area of erythema on the medial dorsum of the left hand four months' previously. This lesion developed into a papule which was followed by central necrosis and crust formation surrounded by an erythematous border There was mild pain and minimal pruritus associated with the lesion The crust fell off within two weeks time resulting in a hyperpigmented area which subsequently became a scar New lesions having a predilection for the inner aspect of the thighs, upper extremities and trunk then developed, which followed a similar course as the original lesion There were from 15 to 20 scattered discrete cutaneous lesions of various sizes which were macular, papular and necrotic

The hemogram revealed 11 per cent monocytes and the tuberculin test was negative with 1 to 100 000 dilution and positive with 1 to 10,000 dilution The bone marrow findings were compatible with lymphosarcoma Histologic examination of a papular lesion disclosed reticulum cell lymphosarcoma and that of a scalene lymph node showed chronic lymphadenitis

XI.

TREATMENT

LYMPHOSARCOMA is, as a rule, extremely radiosensitive A bulky tumor mass may regress to half its size after a few days of treatment and completely disappear within a week Recurrence is rare in areas adequately treated, although new evidence of the disease occurs in other areas Sugerbaker and Craver (130) found, among 108 patients treated by some method of irradiation, that 15 (13 9 per cent) survived for five or more years, but of this number only eight (7 4 per cent) were apparently cured Extirpative surgical procedures were done on 25 patients in 11 removal of an extranodal primary site (such as tonsil, breast or ileum) was done, lymph node dissection in 12 and removal of both an extranodal primary and an adjacent involved lymph node group in two cases With all but a few of these patients surgical treatment was shortly followed by local external irradiation given prophylactically Of these patients six (24 per cent) were living and apparently "cured" five or more years later There were 62 patients who, on admission were considered to have a comparable amount of clinical disease, although in some instances not as anatomically accessible treated by some form of radiation Of these 16 per cent survived for five years but only eight per cent were apparently "cured" The small number of patients in these two groups prohibits any definite conclusions but, they believed further trial of combined surgical and radiologic approach in early cases should be encouraged

The efficacy of roentgenotherapy in prolonging life is questioned by Desjardins and Ford (34), except in cases where life is immediately threatened by the occurrence of mediastinal compression intestinal obstruction or some other acute com-

plication Minot and Isaacs (102) reported a slightly longer survival rate among treated, as compared with untreated patients 2 88 and 2 45 years, respectively They concluded that therapy was of benefit in some cases destined to experience an acute course, but was probably without influence on disease of a more chronic nature

Although the initial response of reticulum cell lymphosarcoma to radiation may be good, the ultimate prognosis is generally regarded as unfavorable according to Hellwig (69a) and Jenkinson *et al* (76) Eight cases of reticulum cell lymphosarcoma having an average two year survival following radiation therapy, were reported by Jenkinson *et al* Stout (129), who reported 89 cases of reticulum cell lymphosarcoma, found no instance of ten year survival in patients under 30 years of age and only 12 1 per cent of all the patients survived for as long as five years

Although irradiation is the preferred treatment for reticulum cell lymphosarcoma at the present time surgical procedures have also been advocated Gall (57a) reported nine cases of stem cell lymphoma in which treatment was by complete surgical excision The median duration of survival was five years Hellwig (69b) reported two patients treated by radical surgery who were living and free of the disease 20 and 10 years later Jackson (75a) stated that if reticulum cell sarcoma is localized to an accessible region excise widely and hope for the best' Holmes and Schulz (71) reported two patients having single lesions of stem cell lymphoma at the time of radiation therapy who were alive and free of the disease more than five years after treatment They noted that long survivals do not occur in patients with multiple lesions Apparently a localized reticulum cell lymphosarcoma aggressively treated, offers a better prognosis than one in which multiple lesions were already present before treatment was begun Irradiation is employed primarily as a palliative measure in cases of generalized disease

There have been encouraging reports on the results of nitrogen mustard therapy for generalized reticulum cell lympho

sarcoma Eichenlaub and Olivos (40) patient had regression of cutaneous and visceral lesions following nitrogen mustard therapy but died from a toxic reaction caused by the drug Goodman *et al* (63) reported a patient with lymphosarcoma whose condition was improved by the administration of nitro gen mustard but who died 12 days later from pneumonia fol lowing agranulocytosis Autopsy disclosed no evidence of lymphosarcoma Other investigators including Craver (29a b c) and Rhoads (114) concluded that the use of nitrogen mustard offered little in the treatment of reticulum cell lymphosarcoma except for palliative effect when irradiation had failed

A patient who improved with oral nitrogen mustard (tri ethylene melamine) was reported by Karnofsky *et al* (79) This 44 year old woman had cutaneous nodules hepatospleno megaly and enlargement of the abdominal and cervical lymph nodes Although the cutaneous lesions responded to roent genotherapy new nodules continued to appear One year later she was given 8 mg of triethylene melamine with decided clinical improvement and regression of the cutaneous lesions and lymph nodes However severe and prolonged bone mar row depression with bleeding resulted and repeated blood transfusions were required for three months The cutaneous lesions then gradually recurred and an enlarged supraclavicular lymph node appeared Six months later triethylene melamine was administered and the cutaneous nodules promptly de creased in size and vascularity The left supraclavicular lymph node became smaller but four months later another appeared on the right side These lymph nodes promptly regressed with local irradiation and the patient continued in excellent condi tion

Osborne *et al* (105) reported a dramatic immediate re sponse to nitrogen mustard therapy in a 61 year old man who had lymphosarcoma There was no gross or microscopic evi dence of lymphosarcoma in the skin or other tissues 12 days after treatment

Despite some enthusiasm for radioactive phosphorus therapy

a decade ago (Kenney *et al* 81), it has been found to have little place in the treatment of lymphosarcoma, according to Diamond (35)

Cutler (30) stated that the actual distribution of lymphosarcoma is nearly always wider than clinical examination discloses, and consequently the presence of the disease in wide areas, not clinically demonstrable, must be suspected and irradiation therapy administered

The treatment of lymphosarcoma cutis is dependent upon whether it occurs as a primary or a secondary manifestation of the disease For the treatment of primary lesions, roentgenotherapy in doses of 3,000 r in air is advocated For secondary lesions, smaller doses of roentgen rays may be used, since the lesions are then merely part of a generalized disease process and nitrogen mustard therapy may be administered

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PART FOUR

IMMUNOLOGICAL STATUS OF THE MALIGNANT LYMPHOMAS

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IMMUNOLOGICAL STATUS OF THE MALIGNANT LYMPHOMAS

It is well known that the reticuloendothelial system is intimately concerned with antibody production (2, 9 11, 13a, b, 18 32) In view of the fact that the reticuloendothelial system is the tissue predominantly involved in the lymphomas, some disturbance of the antibody production might be postulated There is considerable experimental evidence to indicate this theory may be correct

In 1904 Reed (23) noted a negative tuberculin reaction in five out of eight patients having Hodgkin's disease There were 22 negative reactions in 24 cases of Hodgkin's disease reported by Bastai (1) in 1928 He found titers as low as 1 30 and a weak positive reaction in two cases He also observed that a negative reaction had no relation to the duration or severity of the disease and that occasionally a negative reaction became positive following remission induced with roentgen rays

Morquio (19) in 1930, reported that patients having concurrent Hodgkin s disease and tuberculosis reacted negatively to tuberculin I have observed one patient with Pott s disease and sarcoidosis who showed a negative reaction to tuberculin Another patient who had tuberculous pleural effusion and chronic lymphocytic leukemia reacted negatively to full strength tuberculin

A further contribution by Steiner (29) in 1934 indicated that negative cutaneous reactions to both avian and human tuberculin proteins occurred in patients with Hodgkin's disease He modified the usual technic by using tuberculin protein rather than old tuberculin and by employing three different titers on each patient namely, 1 10 000 1 1,000 and 1 100 His results were essentially the same as those of earlier workers in that he

tervals, showed a lessening in intensity, prior to complete disappearance of the reaction, thus indicating a progressive loss of allergy rather than abrupt cessation The performance of multiple tests in these cases enabled them to note a shift in the percentage of positive reactors from the initial 19 per cent to 12 per cent, a change due to rearrangement of statistics to include four patients, who had first been positive, to the group of negative reactors

Schier (27) reported the cutaneous reactions to the antigens of mumps virus, Candida albicans, Trichophyton gypseum and purified protein derivative of tuberculin in 33 patients having Hodgkin's disease These studies revealed a striking cutaneous anergy although the cutaneous reaction to histamine was normal

It would then appear that the statement of Parker *et al* (22) that, Practically all authors are agreed that by far the greatest majority of cases of Hodgkin's disease give a negative reaction, even in cases with an associated active tuberculosis," is essentially correct

Other diseases of the reticuloendothelial system, such as the leukemias and lymphosarcomas, may show a low incidence of positive reactions to tuberculin tests and may be due to a blocking out of that system with resulting anergy, according to Parker *et al* (22) Mycosis fungoides, a disease of the reticuloendothelial system shows a low incidence of positive reactions to the tuberculin test In reviewing 15 patients with mycosis fungoides on whom tuberculin tests were done, Rosenthal (24a) found that 13 patients reacted negatively, and he later (24b) reported that 80 per cent of mycosis fungoides patients will react negatively to the tuberculin test Marten stein and Noll (20) found four out of five patients with mycosis fungoides reacted negatively to 1 5,000 tuberculin and one patient reacted positively

The question now raised is whether this "total anergy" present in the lymphomas is purely a secondary phenomenon or whether it is a primary disturbance, as suggested by Dubin (10) Proponents of the first hypothesis (Morquio 19, de

found repeated testing of the same patient showed negative reactors remained negative following roentgenotherapy, positive reactions were weak and subsequent larger doses induced a reaction no greater than did the smaller dose

The development of anergy in tuberculous patients with concurrent Hodgkin's disease was reported by de Marval (7) in 1940 He attempted immunization with BCG vaccine but failed to produce a positive tuberculin reaction He found that injections as large as 2 cc of crude tuberculin could be given with no apparent reaction and his patients also proved to be anergic to avian tuberculin

This phenomenon of tuberculin anergy was confirmed in 1947 by Dubin (10) who did tuberculin skin testing on 28 adults and 10 children having Hodgkin's disease The results were positive in only one patient who showed a one plus reaction to a 1 100 dilution These results are far lower than the 50 per cent positive reactions usually found Dubin also noted that these same patients had a "weak" positive reaction to the Wassermann test and pointed out that their protection of protective antibodies against typhoid and brucella infection was below normal

In reviewing 150 cases of Hodgkin's disease, Bostick (4) found that the tuberculin test had been performed on 34 patients, 31 of whom showed a negative reaction and three a positive reaction Of 57 patients with Hodgkin's disease tested with tuberculin by Rottino and Hoffmann (26), three patients (5 per cent) gave a positive reaction to 1 10 000 dilution, and eight patients (14 per cent) reacted positively to a 1 100 dilution This was a total of 19 per cent positive reactions in Hodgkin's disease patients as compared with 37 per cent positive reactions among the control patients among whom 42 (17 per cent) reacted to 1 10,000 and 49 (20 per cent) to 1 100 dilutions In none of the negatively reacting patients was the allergy regained, even during induced remissions with roentgen ray or nitrogen mustard therapy The relative paucity with which allergy may be lost is mentioned by Rottino and Hoffmann It occurred within two months in one case and two patients, who were subjected to repeated testing at short in

in most patients with chronic leukemia (28). Davidsohn (6) confirmed these findings and he observed normal or even slightly elevated titers in patients with acute leukemia and following roentgenotherapy, in patients with chronic leukemia. Evans (12) demonstrated a depressed antibody response to typhoid vaccine in patients with lymphomas and leukemias but not in patients with other malignant tumors. Immunization with pneumococcal polysaccharides was used by Larson (16) who found little or no antibody formation in patients with chronic lymphocytic leukemia and multiple myeloma, slightly higher than normal antibody levels in chronic granulocytic leukemia and exceedingly high antibody production in those with acute leukemia. The latter response could be suppressed with cortisone.

On the basis of previous reports and from his own investigations Dubin (10) concluded that patients with Hodgkin's disease exhibit poor immunologic response. He emphasized the "poverty of immunological mechanism" in these patients and commented that although their anergy to tuberculin is well known the concept of this failure of reactivity should include a poor response to all types of antigens. He found the poverty of their antibody production mechanisms" manifest in the inability to produce antibodies fixed to cells (as in tuberculin hypersens [illegible]

such as

Rottino

Hodgkin's disease were capable of producing typhoid agglutinins although in the advanced stage of this disease they were unable to maintain agglutinin levels for more than three months. They later confirmed these findings on the presence of an anergic state to tuberculin in the majority of patients with Hodgkin's disease.

Increase in Susceptibility to Infection. An interesting parallel to the anergy of antigen reactions is the increased susceptibility of these patients to various intercurrent infections according to Dubin (10). Many different bacteria have been isolated and this greater susceptibility to infection seems para

Marval (7) argue that in Hodgkin's disease, or any chronic lymphoma, the reticuloendothelial system is replaced by lymphomatous tissue, thus interfering with its capacity to produce antibodies. On the other hand, Dubin (10) suggested that anergy may be a primary phenomenon. In Hodgkin's disease the fundamental difference may be a primary metabolic dysfunction resulting in a deficiency of the enzyme system, or systems, necessary for proteolysis and proteosynthesis which occurs in antibody production. On the basis of this deficiency, one of many antigenic stimuli may set up a proliferation of reticuloendothelial tissues in an attempt to increase the cells which ordinarily produce antibodies. This reticuloendothelial hyperplasia would normally result in increased antibody production, but in Hodgkin's disease there is merely a futile proliferation of functionless tissue. The cells are present, but their enzyme systems are deficient. According to this hypothesis, one would not expect to find a single etiological agent. It should be remembered that the body has a limited number of ways of responding to injury, as illustrated by the multiplicity of stimuli which produce the response known as "inflammation."

Depression of Antibody Formation. Although the exact mode and site of antibody production is a debatable question, it appears evident that the lymphoreticuloendothelial system participates in this process (9, 11, 13a, b, 18, 32). It has been postulated that anergy associated with reticuloendothelial system diseases results from a blockage of this system, in lymphomas as well as in sarcoidosis. Studies of animals having an adequately blocked reticuloendothelial system have proved that the ability to produce antibodies and to react to antigens are both impaired (5, 30). There have been several reports of depression of antibody formation in patients having lymphomas or leukemias. The Widal reactions were found to be negative in leukemic patients either with typhoid fever or after typhoid vaccination (14, 21), and those who failed to produce agglutinins for sheep erythrocytes after the injection of horse serum (31). Low titers of iso agglutinins were noted

thelial system Borrie (3) stated that, since in both conditions the immunological agents themselves are so variable, it appears more likely that the phenomenon is dependent upon the constitution of the individual rather than on his particular disease In normal individuals who are tuberculin negative about 10 per cent do not become tuberculin positive after BCG vaccination Therefore, Borrie suggested that the incidence of these granulomatous conditions may be greater in these individuals than in the general population and is possibly due to their immunological state

It was our belief (251) that a study of certain immunological reactions in patients having cutaneous lesions due to diseases of the leukemia lymphoma group would prove to be of interest in two ways 1) To determine from a pathogenic standpoint, whether the conditions were immunologically homogeneous thus pointing to a possible etiologic and pathogenic relationship and 2) To determine whether there is a disturbance of antibody production since, from an immunological standpoint lymphoreticular tissues are intimately concerned with antibody production Because the tissue primarily involved in lymphomatous disease is lymphoreticular tissue, some disturbance of antibody production could be anticipated a fact indicated by considerable experimental evidence We were primarily concerned with the persistence of cutaneous reactivity to antigens which these patients had presumably been exposed to prior to onset of the disease

It was found that there is a general depression of reactivity to the antigens more marked for the delayed type One conclusion was reached regarding immediate reactivity The substrate for development of an immediate type of allergic reaction is not impaired in that these patients showed normal reactions to histamine and to a histamine liberator

There is therefore, a general depression of the delayed type of allergic reactivity to antigens to which these patients had presumably been exposed and to which, it may be assumed, they were at one time sensitive

With our present knowledge concerning the underlying

doxical in the presence of the massive proliferation of reticulo-endothelial tissues, these cells being the antibody producers

It is now the general opinion that tuberculosis is a complication of Hodgkin's disease and sarcoidosis in 15 to 25 per cent of the cases and it is not the exciting factor, as was formerly believed

Desjardins (8) was impressed by the great frequency of infections of various types among Hodgkin's disease patients In all probability, this is due to the poor immunological mechanism which results in the higher frequency of intercurrent infections and increased susceptibility to infections This also accounts for the finding of various bacteria in these patients and explains why the tubercle bacillus, diphtheroid bacillus, brucella and other bacteria have sometimes been found in tissues of these patients

BCG Vaccination. Borrie (3) recently reviewed the subject of BCG vaccination in diseases of the reticuloendothelial system De Marval (7) was unable to procure conversion with BCG vaccination in his cases of Hodgkin's disease Similar findings were reported in a case of histoplasmosis by Lemming (17) We have been unable to procure conversion with BCG vaccination in two patients having mycosis fungoides

The fact that the majority of sarcoid patients have negative tuberculin skin reactions, and that this tuberculin anergy is not affected by BCG vaccination, can no longer be used to support the concept that sarcoidosis is a peculiar response to the tubercle bacillus Similar phenomenon are found in Hodgkin's disease mycosis fungoides and histoplasmosis Furthermore, in sarcoidosis, immunological response to antigens, other than those of the tubercle bacillus is also depressed as, for example, to pertussis vaccine (15) Similar results are found in Hodgkin's disease with regard to spirochetal, typhoid and brucella antigens according to Dubin (10)

The fact remains that in certain chronic granulomatous conditions there is a nonspecific depression in immunological response and it is frequently suggested that this phenomenon can be explained as being due to damage to the reticuloendo

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mechanisms in development of delayed allergic reaction, any discussion regarding one sensitive individual's subsequent failure to react must be purely speculative There is some evidence to support the belief that the essential change in development of this type of sensitivity is an enzymatic adaptation to the antigen It is believed that this enzymatic adaptation takes place in the primitive reticulum cell and is passed on to its descendants Therefore, it is suggested that in diseases affecting the primitive reticulum cell or its descendants, there may be impairment in the ability to perpetuate this enzymatic adaptation (it is usually agreed that lymphoid and myeloid cells are derived from this cell type) or in the ability of the diseased cell to react to the antigen which originally engendered the adaptation or, finally, the enzymatic adaptation itself could be lost In any of these situations a reduction or absence of the delayed type of allergic reactivity would result It was suggested that lack of delayed type of allergic reactivity in the diseases which were studied could probably be explained on this basis

As a result of our investigations (25b), we were able to show 1) that patients having a lymphoma leukemia disease accept passive transfer (Prausnitz-Kustner reagin) and react normally to the specific allergen against this antibody and, 2) that such individuals have an impaired ability to develop an allergic eczematous sensitization to a simple chemical It is believed that this defect occurs because of a specific effect of the disease process on the cells of the lymphoreticular system, inasmuch as a control group consisting of patients having a chronic, severe illness were apparently able to develop an eczematous sensitization to the same simple chemical It was suggested that the lymphomas, by virtue of affecting the cells of the lymphoreticular system (the cells concerned with a variety of immunologic processes), caused an impairment in all types of delayed allergic reactivity

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